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2. Hicken, N. F., Stevenson, U. L., Franz, B.J., Crowder, Earl: *Amer. Jour. Surg.*, 78:347, Sept., 1949.

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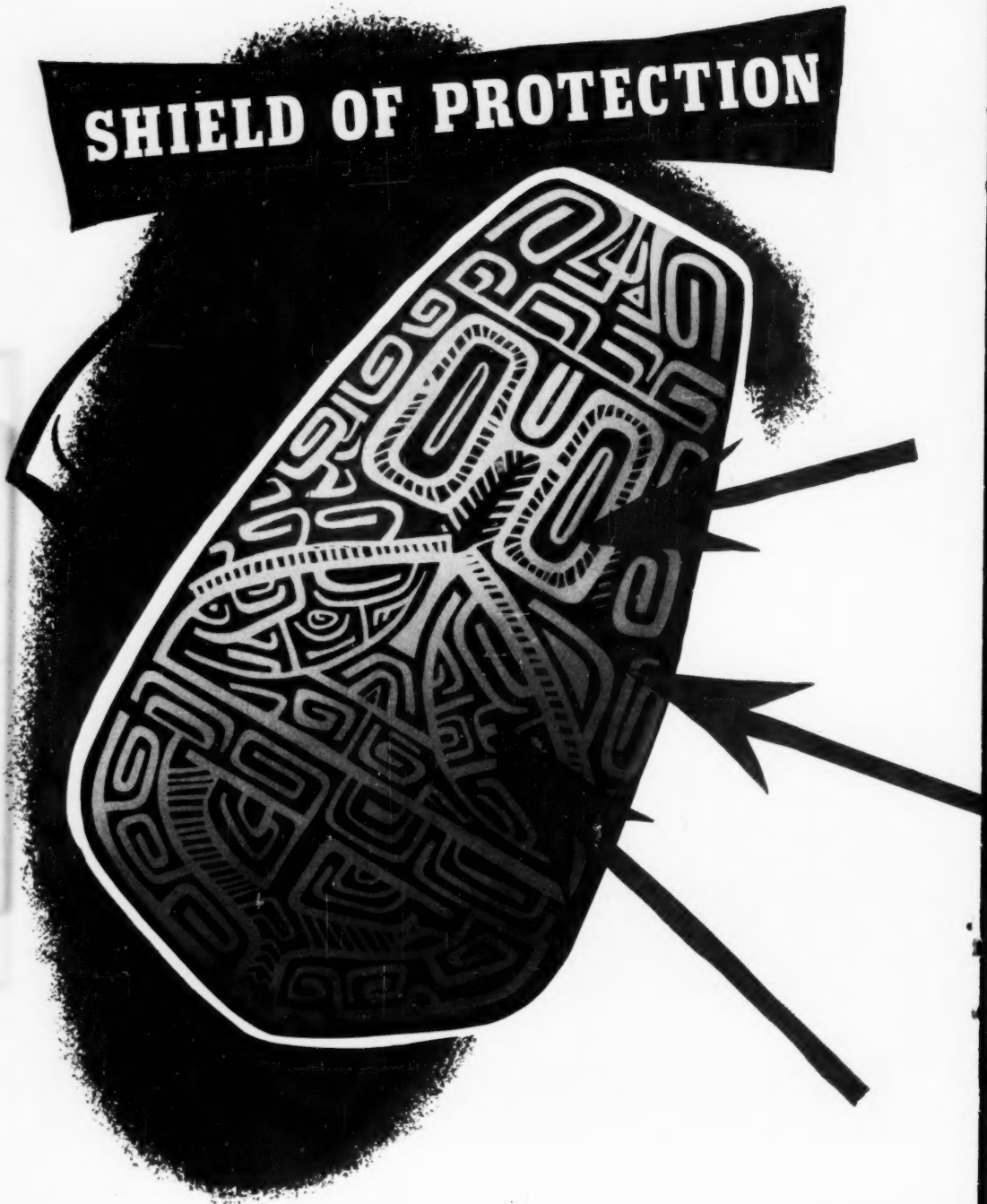

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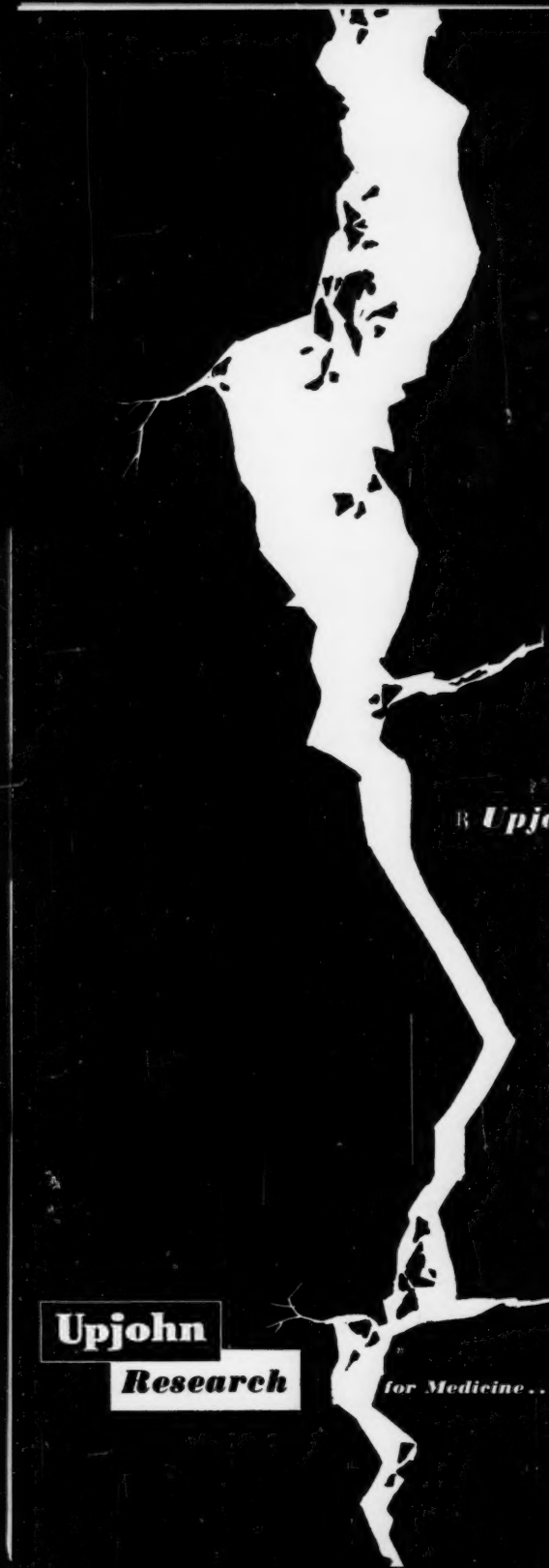

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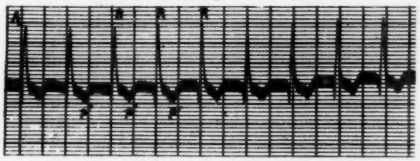
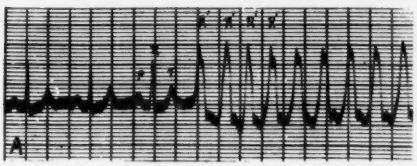
Glycoside Therapy of Refractory Paroxysmal Arrhythmia

Auricular paroxysmal tachycardia is a relatively common disorder. Many attacks are brief and cause no harm. On the other hand, some persist for hours or days and, if not treated, may precipitate heart failure. In rare instances attacks have even caused death.[1,2]

Diagnosis: In the adult subjective symptoms give the first clue to diagnosis. Clinically, heart beats are irregular in tachycardia of ventricular origin, while they are regular in the auricular tachycardia. An electrocardiogram taken during an attack aids differential diagnosis.[1,3] (See illustrations.)



Electrocardiogram. (Lead 2) of Auricular paroxysmal tachycardia — usual mechanism; from White.[3]



Electrocardiogram. (Lead 2) showing Ventricular paroxysmal tachycardia — usual type onset; from White.[3]

Paroxysmal tachycardia also occurs in infants. Levine[4] states that although lack of subjective observations in such cases causes difficulty, its detection is highly important because ". . . treatment may well be life-saving."

Treatment: To terminate a persistent paroxysm vagal stimulation by some simple measure, such as gagging, body bending or pressure on a carotid sinus is effective in about 10% of cases. Until recently the remaining cases had to be treated with either quinidine or mecholyl, neither of which is entirely reliable or free of toxicity.[1,2,3]

As Barrow[2] has stated, "The drug used should be non-toxic, rapid in action, and certain in its effect."

Lanatoside C,* a crystalline digitalis glycoside, has pharmacologic qualities which measure up closely to the action desired. It is rapid in action, and dissipates quickly, thus being ideally suited for the short-term action needed in these cases. (Table I.) Tandowsky,[5] Weisberger and Feil,[6] Barrow,[2] and Levine[4] report independently that Lanatoside C* intravenously is uniformly effective in terminating paroxysms without toxic side reactions. In a series of 16 cases, Weisberger and Feil observed reversion to normal rhythm within 40 minutes in all but one case. In Barrow's series arrhythmia stopped in all cases within 1½ hours. Tandowsky[5] found Lanatoside C* orally also of value to prevent further paroxysms after intravenous therapy has been given to stop an attack.

Lanatoside C* dosage to terminate an attack ranges from 0.8 mg. to 1.6 mg. i.v.; Prophylactic dosage: 0.5 to 1.0 mg. daily by mouth. Levine's[4] i.v. dose in infants: 0.01 mg. per pound of body weight; repeated twice at 25-minute intervals, if necessary.

TABLE I

	LANATOSIDE C	DIGITOXIN	DIGOXIN	OUABAIN
RATE OF I. V. ACTION	1 – 2 hrs.	6 hrs.	1 – 2 hrs.	1 hr.
DURATION OF ACTION	2 – 10 dys.	14 – 21 dys.	5 – 7 dys.	1 – 4 dys.
RATIO: DOSE CAUSING TOXICITY (ORAL)	1.5 to 2.0 mg./dy.	0.2 to 0.3 mg./dy.	1.0 mg./dy.	Not Useful Orally
RATIO: THERAPEUTIC MAINTENANCE DOSE (ORAL)	1 mg./dy.	0.1 mg./dy.	0.5 mg./dy.	Not Useful Orally

Based on a report presented by G. F. Schmitt at the Florida State M. A., 1950. Data on Toxic: Therapeutic Ratio from Batterman, R. and DeGraff, A.: Amer. Heart J.: 34: 663 (Dec.) 1947

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1. Christian, H: Diseases of the Heart. Oxford Univ. Press, 1940, p. 424. 2. Barrow J.: Ann. of Internal Med. *32:* 116, 1950. 3. White, P.: Heart Disease, Macmillan Co., 1949, pp. 868, 872. 4. Levine, E.: Calif. Med., *72:* 91, 1950. 5. Tandowsky, R.: Am. Heart J., *29:* 71, 1945. 6. Weisberger, A. & Feil, H.: Heart J. *34:* 871, 1947.

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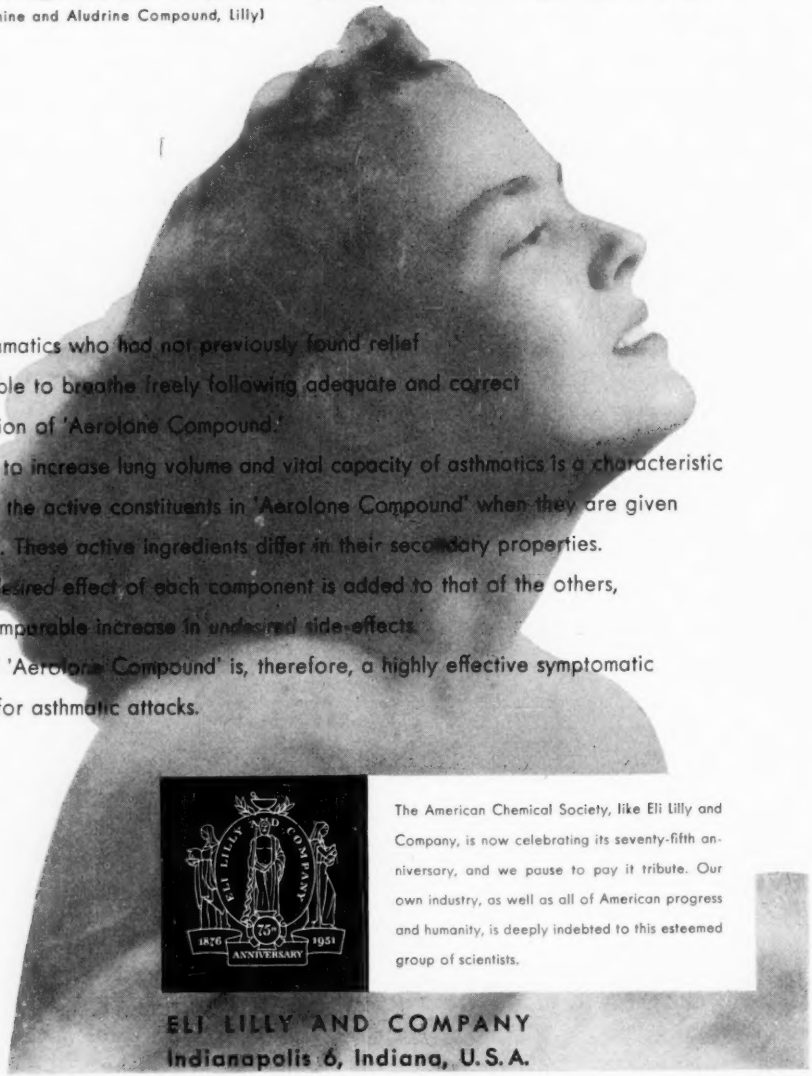

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THE EFFECT OF THE INTRAVENOUS ADMINISTRATION OF DEXTRAN ON CARDIAC OUTPUT AND OTHER CIRCULATORY DYNAMICS [1]

By A. C. WITHAM, J. W. FLEMING, AND W. L. BLOOM

(From the Medical Service, Lawson VA Hospital, Chamblee, Georgia, and the Department of Medicine, Emory University School of Medicine, Atlanta, Georgia)

(Submitted for publication February 14, 1951; accepted June 18, 1951)

INTRODUCTION

It has been well established that partially hydrolyzed dextran is effective in expanding and maintaining the plasma volume (1–3). Previously, there have been numerous investigations concerning the effects of plasma volume expansion on the circulatory dynamics (4–7). Many of these studies have used saline or plasma protein preparations. The former only temporarily expands the plasma volume and then rapidly distributes itself in the extracellular fluid; whereas the plasma protein has a more permanent intravascular residence. Other investigators have utilized solutions of gelatin (8), gram arabic, and acacia.

Dextran provides another opportunity to study the effects of hemodilution and plasma volume increase on certain physiological aspects of the circulation. Investigations of this nature have been reported by Bull and associates (2) on two patients studied with the cardiac catheter during a surgical operation.

Using the dye dilution technique (9, 10) for determining cardiac output also provides a unique opportunity to study the effect on the pulmonary circulation associated with blood volume expansion.

Data to be presented show that dextran consistently increased the plasma volume proportionally to the amount administered and that the effect was prolonged. Cardiac output was increased in every case. The increased plasma volume was associated with prolonged elevations of pressure in the pulmonary circulation.

[1] Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or the policy of the Veterans Administration.

METHODS

The patients were studied in the fasting state. All were male, and their ages ranged from 22 to 44. Diagnoses and a summary of important data are listed in Table I. All of the patients with lung disease were afebrile, well hydrated, and their lesions were well localized. The partially hydrolyzed 6 per cent dextran [2] solution had a viscosity of 3.31 centistokes at 25° C and was made up in 0.85 per cent saline.

Pulmonary artery catheterizations were performed with a 6-F and 8-F intracardiac catheter. The systemic arterial blood samples and pressure records were obtained from an indwelling, femoral arterial needle. An electromanometer (Sanborn), recording through a single channel, direct-writing electrocardiograph (Sanborn) was used for all pressure tracings. Arbitrary reference point was 5 cm. below the level of the sternal *angle of Louis*. Mean pressures were obtained by electrical integration of the pulse contours. Pulmonary "capillary" pressures were obtained as described by Hellems, Haynes and Dexter (11).

Cardiac outputs were derived by the method of Hamilton (9, 10), using Evans Blue dye (T-1824). Concentration of the dye in the plasma was determined according to the method of Dow and Pickering (12). Dye output determinations have been shown to correlate well with the Fick procedure (13). A figure ("Q") was also derived from the dye curve as an index of pulmonary blood volume, as described by Ebert and co-workers (14). "Q" includes the blood volume in the lungs, left heart, aorta, and certain large arteries. Pulmonary arteriolar resistance and cardiac work were calculated according to the formulae mentioned by Dexter and associates (15).

Blood volume was determined according to the method of Gibson and Evans (16). Specimens were obtained 10 minutes following the injection of Evans Blue dye. Estimated changes in blood volume after dextran were made by assuming that the changes were proportional to the percent of changes in hematocrit. However, Leard and Freis (17) have shown that this method failed to show accurate quantitative changes in patients excessively hydrated over a period of five days, when blood volume determinations were done by the dye method before and after hydration. However, the hemodilution which occurs following dextran injection has been shown to be

[2] Supplied by Commercial Solvents Corporation.

TABLE I

Patient	Body surface area, sq. m.	Cardiac output, L/min.	Cardiac index, L/sq. m./min.	Pulse rate/min.	Stroke volume, cc.	Circulation time, secs.			"Q," cc.	Pulmonary artery pressure, mm. Hg			Mean pulmonary "capillary" pressure, mm. Hg	PA–"PC" gradient, mm. Hg	Pulmonary resistance, dynes sec. cm.$^{-5}$	Peripheral resistance, dynes sec. cm.$^{-5}$	"Work," kg. m./min./sq. m.		Femoral artery pressure, mm. Hg			Hematocrit, cc.	Per cent change in hematocrit	Blood volume, cc.	Estimated change in blood volume	Venous pressure, mm. H_2O	Diagnosis
						Lesser	Mean	Total		Systolic	Diastolic	Mean					R. vent.	L. vent.	Systolic	Diastolic	Mean						
1*	1.77	4.8	2.7	80	60	6	11	12	740	18	5	11	3	8	134	1542	.43	3.6	100	74	92	47	—	3960	—	60	Tbc. RUL
†		6.1	3.4	90	67	4	8	9	795	35	16	23	14	9	120	1338	1.18	4.9	130	78	100	40	15	—	590	72	cavity
2*	1.8	4.7	2.6	95	49	4	9	12	662	20	5	13	—	-	—	1199	.46	2.6	100	55	70	43	—	2700	—	—	Lung abscess
‡		5.5	3.1	90	61	6	11	12	960	27	13	20	—	-	—	1046	.88	3.2	100	56	72	—	—	—	—	—	LLL
3*	1.7	4.0	2.4	90	48	6	12	12	806	30	13	16	—	-	—	1832	.54	3.0	140	75	90	48	—	3180	—	—	Labile hyper-
†		5.5	3.3	90	61	4	12	16	1050	33	16	23	—	-	—	1504	1.05	4.8	159	90	103	42	12	—	367	—	tension
4*	1.95	6.1	3.2	90	68	5	12	16	1216	12	6	8	—	-	—	1178	.36	4.2	125	74	90	50	—	5430	—	—	Tbc. LUL
†		9.4	4.8	100	94	5	11	11	1760	16	6	10	—	-	—	785	.69	6.4	130	75	92	45	10	—	543	—	cavity
5*	1.96	5.7	2.9	75	74	6	12	11	1109	20	7	11	6	6	78	1298	.46	3.9	108	78	92	43	—	3862	—	57	Inactive tbs.
†		7.0	3.6	70	99	4	11	14	1280	23	8	14	8	6	63	1103	.69	5.0	115	80	96	39	9	—	360	—	partial
‡		7.3	3.7	70	103	2	11	15	1350	24	10	16	8	8	89	1000	.83	5.0	110	70	90	39	9	—	360	—	collapse
§		6.8	3.5	75	90	6	10	9	1134	26	7	16	8	8	89	1132	.77	4.8	114	80	96	—	—	—	—	67	left lung

* Before administration of dextran.
† 10 minutes after dextran administration completed.
‡ 25 minutes after dextran administration completed.
§ 90 minutes after dextran administration completed.

of the same order of magnitude by both hematocrit and serum protein determinations (18).

Venous pressure readings were made with a Burch-Winsor manometer (19).

The basic experiments were done as follows: the patients were given mild sedation (1 to 3 grains of sodium phenobarbital intramuscularly), the catheter tip passed in the pulmonary artery, and the indwelling, femoral arterial needle inserted. An initial dye injection was made, and several pressure tracings were taken. Patients were tested for sensitivity by the intradermal and conjunctival injection of dextran. Five hundred cc. of 6 per cent dextran were given intravenously at the rate of 25 cc. per minute. Pressure recordings were done midway in the administration of the dextran, immediately after its completion, and at frequent intervals thereafter. Second dye injections were done at about 10 minutes after administration in most cases and at 25 minutes in two cases. A third dye injection was made after 90 minutes in the last case. There were no untoward reactions to dextran.

TABLE II

Average determinations before and after dextran administration

	Before	After
Cardiac output (L/min.)	5.06	6.76
Cardiac index (L/min.)	2.70	3.65
Pulse rate (beats/min.)	86	88
Stroke volume (cc./stroke)	60	75
Pulmonary artery pressures (mm. Hg):		
Systolic	20	26
Diastolic	7	12
Mean	12	18
Blood volume (cc.)	3826	4291
"Q" (cc.)	800	1099
Femoral artery pressures:		
Systolic	114	122
Diastolic	71	76
Mean	87	93
Venous pressure (mm. water)	58	69
Work (kg. m./min./sq. m.):		
R. ventricle	.465	.923
L. ventricle	3.39	4.79
Circulation time in secs.:		
Lesser	5	4.2
Mean	11	10.4
Total	12.5	12.4

RESULTS

As shown in Tables I and II and in Figure 1, there were increases in cardiac output in every case following the administration of dextran. There was an average rise of 38 per cent if determinations were done within 10 minutes after injection. The change in stroke volume was commensurate with this increase, but the average pulse rate showed no appreciable change.

As illustrated in Figure 2, when dextran was given, there was a gradual rise in pulmonary artery pressure during the infusion. The peak rise was noted immediately after the completion of the dextran administration. There was usually a gradual decline in the pressure; however, the peak was maintained for only 12 to 20 minutes in two

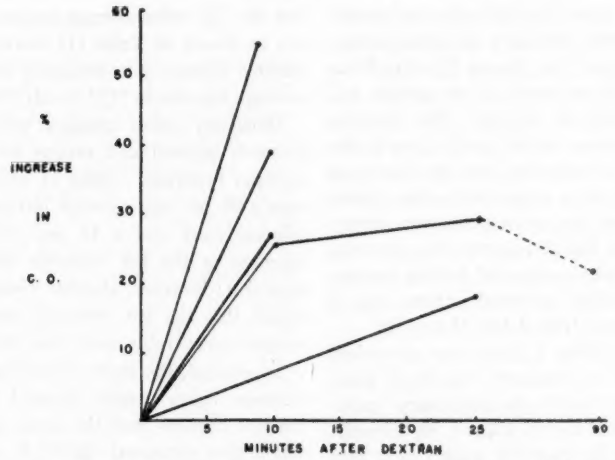

FIG. 1. PER CENT CHANGE IN CARDIAC OUTPUT AFTER 500 CC. DEXTRAN

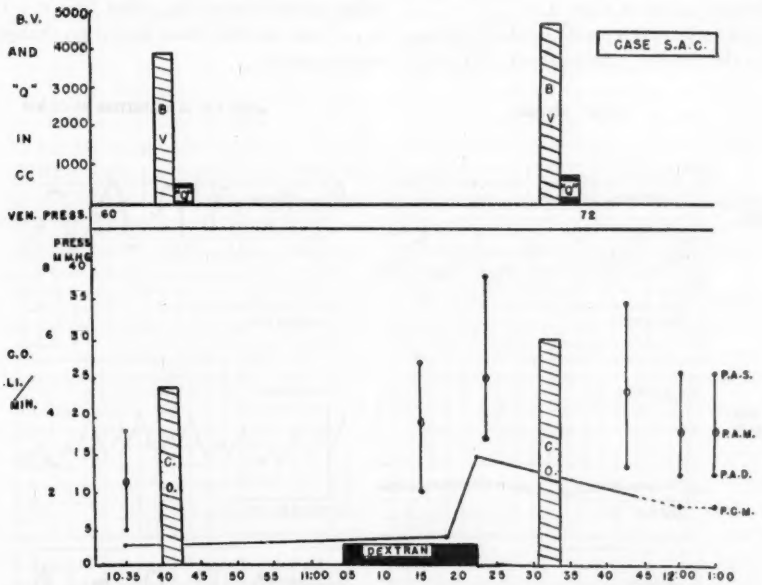

FIG. 2. HEMODYNAMIC CHANGES FOLLOWING INFUSION OF 500 CC. OF DEXTRAN, AS OBSERVED IN CASE 1

C.O. = cardiac output
B.V. = total blood volume
"Q" = index of pulmonary blood volume
P.A.S. = systolic pulmonary artery pressure
P.A.M. = mean pulmonary artery pressure
P.A.D. = diastolic pulmonary artery pressure
P.C.M. = pulmonary "capillary" mean pressure

cases, then fell to lower but still elevated levels. Four patients showed increases in mean pulmonary artery pressure of 5 to 10 mm. Hg after 45 to 90 minutes, and the pressure in one patient fell to normal limits after 32 minutes. The rise was due to a greater increase in the systolic than in the diastolic pressure in three cases, and the rises were about the same in both pressures in two cases. The average rise in the mean pulmonary artery pressure was 6 mm. Hg 10 minutes after dextran, at which time the dye was injected, but the average mean peak rise, which occurred earlier, was 9 mm. Hg, with a range from 4.5 to 15 mm. Hg.

As recorded in Table I, there was a marked and prolonged rise in pulmonary "capillary" pressure in Case 1. In Case 5, the pulmonary "capillary" pressure rose from 6 to 13 mm. Hg immediately after dextran but then fell quickly to a very slightly elevated level. Figure 3 illustrates the pressure changes noted in Case 1.

The average estimated increase in blood volume was close to the amount administered (500 cc.), but the "Q" value average increase was about 300 cc., as shown in Table II; however, if Case 4 is omitted because of its unusually large increase, the average increase in "Q" is only 192 cc.

Relatively small changes were noted in the systemic arterial and venous pressure following dextran injection. Table II indicates that there was a 98 per cent average increase in right ventricular work and a 41 per cent average work increase of the left ventricle following dextran injection; however, absolute changes in work indicate that the left ventricle increases its work output considerably more than the right ventricle.

In general, the lesser circulation and total circulation times usually showed no constant or marked changes, and the mean pulmonary circulation time decreased slightly in most cases.

Studies on two of our patients and on numerous other patients receiving either 500 or 1000 cc. of 6 per cent dextran have shown no changes in the vital capacity.

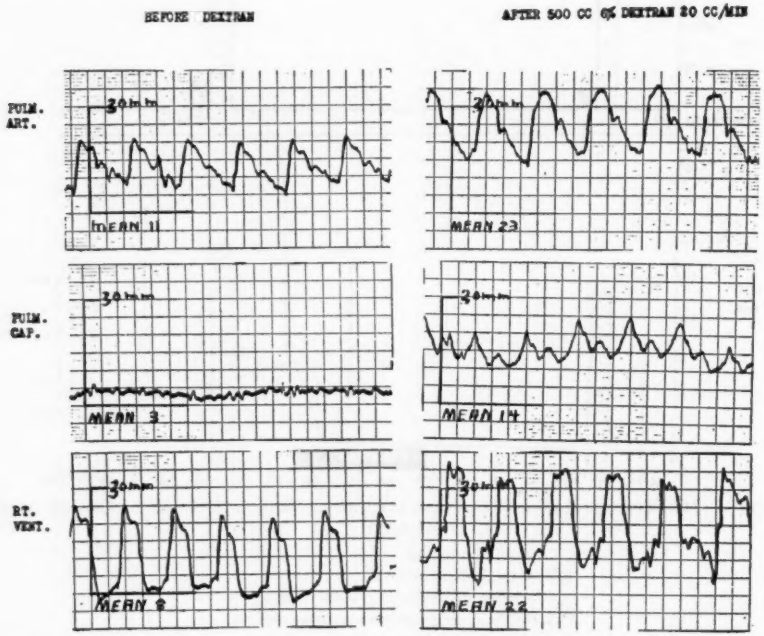

FIG. 3. PULMONARY ARTERY, PULMONARY "CAPILLARY," AND RIGHT VENTRICULAR PRESSURE RECORDINGS NOTED BEFORE AND 10 MINUTES AFTER THE ADMINISTRATION OF 500 CC. OF DEXTRAN TO CASE 1

DISCUSSION

There have been conflicting reports concerning the ability of increased blood volume to enhance consistently the cardiac output in normal subjects. Whereas McMichael and Sharpey-Schafer (4) have stated that elevations in diastolic filling pressure will produce an increase in cardiac output in man, Warren and associates (5) have denied that this occurs regularly in normal humans when the right atrial pressure is increased by intravenous saline or human serum albumin. In both of these studies the cardiac output was measured by the Fick principle. Also, Doyle and co-workers (20), using saline and both the dye and Fick procedures, have found no consistent increase in output.

As shown in Figure 1, there was a consistent increase in the cardiac output following dextran in all of our cases using the dye method. Cardiac output was still elevated after 25 and 90 minutes, respectively, in two cases.

While, theoretically, there are several differences between raising the ventricular filling pressure with an osmotically inactive diluent such as saline and doing the same thing with an isotonic and isoncotic fluid such as dextran, it is difficult to see how the albumin and dextran solutions should differ hemodynamically in short term experiments such as these. Actually, in Warren's seven cases given albumin infusions, five had increases in cardiac output. The other two cases had relatively high "basal" outputs with subsequent falls into the normal range after albumin. Dye and Fick methods have been shown to be comparable (13), and it can be seen that our patients had lower basal outputs generally than those in Warren's series.

Hardy and Godfrey (6), using the ballistocardiograph, found that the intravenous infusion of physiological saline solution caused an increase in cardiac output in patients who were dehydrated but produced no change in normally hydrated subjects. Fletcher and associates (7), also using the ballistocardiograph, showed that the intravenous administration of 6 per cent ossein gelatin solution produced a marked increase in minute volume output in very debilitated patients, but the change in output was not very remarkable in normal patients. All of our patients were well hydrated, and none was debilitated.

Altschule and Gilligan (8), using the ethyl iodide technique for cardiac output, reported that there was a direct correlation between elevation of the peripheral venous pressure and increase in cardiac output. They stated that if over a liter of saline is given intravenously at a rate faster than 20 cc. per minute, normal individuals will respond with a temporary increase in cardiac output. Doyle and co-workers (20) state that their results are inconsistent following infusions of saline at rates of 100 cc. per minute. Our patients received only 25 cc. per minute. That venous pressure is elevated following dextran injection, has been shown by several investigations (2, 3, 18).

It has been reported (1, 2) that during administration of other preparations of dextran, more venous engorgement occurred than is noted with comparable amounts of blood or serum albumin. It was suggested that this resulted from osmotic withdrawal of fluid from the extracellular spaces. This excessive engorgement did not occur with our isotonic, isoncotic preparation of dextran, and the blood volume studies showed only increases comparable to the amount of dextran solution administered.

The data presented here might suggest that in these cases the increases in cardiac output are due to increases in the total plasma volume, resulting in increases in stroke volume.

In the calculation of the "Q" value, it is apparent that the average "Q" increase was around 300 cc. (or about 200 cc. if Case 4 is omitted), while the total blood volume increased only by the amount of fluid administered (500 cc.). It should be pointed out that this disproportionate increase in "Q" does not mean an increase of 300 cc. in the pulmonary blood volume, for the vascular bed of the lung is only a portion of "Q." Cournand (21) believes that the average human lung contains about 400 cc., whereas the average "Q" value is about 1000 cc. In our experience, the pulmonary blood volume index ("Q") usually does not vary more than 15 per cent in repeated determinations in the same patient with an undisturbed circulation. However, others feel that the "Q" determination is inaccurate and that changes of the magnitude mentioned in our discussion may not be significant.

Following the dextran administration, rises in

the peripheral venous pressure were relatively small (10 and 12 mm. H_2O), whereas most pulmonary artery pressure rises were around ten times that amount. Figure 2 shows that changes in mean pulmonary "capillary" pressure almost completely accounted for the rises in mean and diastolic pulmonary artery pressure in that case.

SUMMARY AND CONCLUSIONS

1. A study was made of the effect upon the circulation of increasing the plasma volume by the intravenous administration of 6 per cent dextran in five men.

2. In every case there was a prolonged rise in pulmonary artery pressure and an increase in the cardiac output. The changes in pulse rate and systemic blood pressure were slight and inconsistent.

3. Blood volumes after dextran showed only increases comparable to the amount of solution administered. The dextran used was isoncotic and isotonic.

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ON THE COMPARATIVE PROTHROMBIC ACTIVITY OF HUMAN AND DOG BLOOD[1]

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Soon after the introduction of the one- and two-stage methods for determining prothrombin, it was noted that while the results obtained by the two procedures generally agreed fairly well, marked discrepancies occurred in certain specific instances. Particularly puzzling has been the observation that the prothrombic activity of human blood as compared with dog blood, when measured by the two tests, is markedly different. Warner, Brinkhous and Smith (1) reported that the prothrombin concentration in dog blood is 350 units per cc. and in human blood 295 units. More recently Murphy and Seegers (2) found 190 to 205 units in dog and 290 to 315 in human blood. Mann and his associates (3, 4) reported that the average for dog blood is 183 units per cc. and for human blood 319 units. These findings indicate that the prothrombin concentration as measured by the two-stage method is approximately the same in the two species. When determined by the one-stage method, the prothrombic activity of dog blood, in marked contrast, is many-fold higher than in human blood (5). The reason for this divergency has not been satisfactorily explained, but obviously as long as this problem remains unsolved, a marked gap in the knowledge concerning prothrombin remains. In the present investigation human and dog bloods were studied by means of the prothrombin consumption test and by the adsorption and elution technique for determining prothrombin with the aim of obtaining new data that might be helpful in arriving at a better understanding of what constitutes prothrombic activity.

METHODS

The prothrombin consumption time. The directions as previously outlined were followed (6, 7). In carrying out the prothrombin consumption test on serum from platelet-poor plasma, blood is collected with a silicone-coated needle and syringe, and immediately transferred to silicone-coated test tubes immersed in an ice bath. After the tubes are chilled for 10 minutes, they are centrifuged in an Angle Centrifuge at 8000 r.p.m. for 10 minutes. One cc. of the plasma (having a platelet count less than 3000 per mm.) is transferred to a glass test tube and placed in a water bath at 37° C. The fibrin is removed as it forms by wrapping it about a glass stirring rod. When the coagulation of fibrinogen is complete, the serum is tested every five minutes for its prothrombic activity. Usually it becomes constant in 15 minutes. The prothrombin time is determined as follows: To a mixture consisting of 0.1 cc. deprothrombinized oxalated rabbit plasma, 0.1 cc. thromboplastin and 0.1 cc. 0.02 M $CaCl_2$ solution, 0.1 cc. of serum is added by blowing from a pipette. The formation of the clot is accurately timed.

The determination of prothrombin by the adsorption and elution technique as developed by Stefanini and the writer (8) was followed. In this test the prothrombin is adsorbed with tricalcium phosphate and then eluted with sodium citrate. Since one volume of eluate contains the prothrombin of 10 volumes of plasma, the eluate is mixed with nine volumes of deprothrombinized rabbit plasma for assaying its prothrombic activity. Rabbit plasma has been found to be a satisfactory assay medium because it has a high and constant concentration of labile factor.

RESULTS

A comparative study of the prothrombic activity of human and dog plasmas and sera are recorded in Table I. The prothrombin time of normal human plasma is 12 seconds and of dog plasma six seconds. The same values are obtained when determined by the adsorption and elution procedure. On storing oxalated human and dog plasma in an open container at 4° C., the prothrombin time steadily increases but in human plasma the rise is much more rapid. If deprothrombinized rabbit plasma, which is a rich source of labile factor, is added to the stored human plasma, the prothrombin time is decreased to eight seconds. Likewise, the eluate obtained from aged human plasma yields a prothrombin time of eight seconds. When the labile factor is restored in

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TABLE I

The comparative prothrombic activity of dog and human plasma and serum

Experiment no.		Prothrombin time Direct (sec.)	Prothrombin time Of eluate (sec.)
1.	Dog plasma fresh	6	6
2.	Dog plasma fresh, 9 volumes + Rabbit $Ca_3(PO_4)_2$ plasma, 1 volume	6	6
3.	Dog plasma stored 2 days	8	6
4.	Dog plasma stored, 9 volumes + Rabbit $Ca_3(PO_4)_2$ plasma,* 1 volume	6	
5.	Dog serum from platelet-rich plasma	15	15
6.	Dog serum from platelet-poor plasma	6½	6½
7.	Normal human plasma fresh	12	12
8.	Normal human plasma fresh, 9 volumes + Rabbit $Ca_3(PO_4)_2$ plasma, 1 volume	12½	12½
9.	Normal human plasma stored 2 days	17	8
10.	Normal human plasma stored, 9 volumes + Rabbit $Ca_3(PO_4)_2$ plasma, 1 volume	8	
11.	Normal human serum from platelet-rich plasma	21	21
12.	Normal human serum from platelet-poor plasma	8	8

* Fresh oxalated rabbit plasma treated with $Ca_3(PO_4)_2$.

stored dog plasma, the prothrombin time again becomes six seconds; likewise the eluate has this value. There is, however, no increase in prothrombic activity during storage.

When platelet-rich human or dog plasma is clotted, the serum has a comparatively marked decrease in prothrombic activity. If the plasma is clotted after the removal of platelets, human serum has a prothrombin time of about eight seconds while dog serum has a value of six and one-half seconds. Native plasma, either platelet-rich or poor, from a severe hemophiliac, when clotted in glass yields a serum that has a prothrombin time of eight to eight and one-half seconds. In every instance the direct prothrombin time agrees with that obtained by the adsorption and elution procedure.

DISCUSSION

The simplest explanation for the difference of the prothrombin times of dog and human plasmas is that the former contains a much higher concentration of prothrombin than does human plasma. This conclusion is supported by the finding that on assaying the eluates of dog and human plasmas, it is found that their prothrombin times are six and 12 seconds respectively—the same as found by the direct one-stage test.

Although it has been shown that increasing the labile factor above the minimum level required for optimum prothrombin time does not further shorten it (9), it may still be claimed that the higher concentration of labile factor in dog blood might be responsible for the faster clotting time. When the prothrombin is determined by the adsorption and elution procedure, the labile factor is not a variable, because in the assay of the eluate, a standard amount of deprothrombinized rabbit plasma, which has a high concentration of labile factor, is employed. The close agreement between the results of the direct one-stage and the adsorption and elution method is good evidence that the labile factor does not influence the results of the one-stage method unless it is below the minimal requirement.

When normal dog blood clots, the prothrombin time of the serum increases because most of the prothrombin is converted to thrombin. In the experiment recorded in Table I, Exp. 5, the prothrombin time of the serum is 15 seconds. By means of the prothrombin curve for dog blood obtained by saline as a diluent (7), one can estimate that over 90 per cent of the prothrombin in this serum is consumed. In marked contrast, when platelet-poor plasma clots, the prothrombin time of the serum is practically the same as that of the plasma (Table I, Exp. 6). On account of the lack of platelets, so little thromboplastin apparently becomes available that only a very small amount of prothrombin is consumed. It is to be noted that in serum from both platelet-rich and poor plasma the prothrombin time by the direct one-stage method agrees with the values obtained by the adsorption and elution test. When oxalated dog plasma is stored, the prothrombin time slowly increases, but the eluate from this aged plasma had a prothrombin time of six to six and one-half seconds (Table I, Exp. 3) which clearly shows that no significant change in prothrombin occurs in dog plasma during short periods of storage.

When normal human blood clots, the serum has a prothrombin time which usually ranges from 15 to 30 seconds. This illustrates that, as in dog blood, much of the prothrombin is consumed during clotting. Fresh native plasma depleted of platelets by high centrifugation when clotted in glass yields a serum which has a prothrombin time of about eight seconds (Table I, Exp. 12). Significantly, the serum obtained from the clotting of

TABLE II

The changes in prothrombic activity observed in hemophilic blood on storage and after clotting

Experiment no.	Prothrombin time Direct (sec.)	Prothrombin time Of eluate (sec.)
1. Hemophilic plasma fresh*	12	12
2. Hemophilic plasma stored 2 days	18	8
3. Hemophilic plasma stored, 9 volumes + Rabbit $Ca_3(PO_4)_2$, 1 volume	8	
4. Hemophilic serum from platelet-rich plasma	8–9	8–9
5. Hemophilic serum from platelet-poor plasma	8	8

* From a severe hemophiliac.

plasma of a severe hemophilic subject likewise has a prothrombin time of eight seconds even when the platelets are not diminished (Table II, Exps. 4 and 5). Furthermore, both normal and hemophilic blood when stored 24 to 48 hours have a prothrombin time of approximately eight seconds. Thus, a marked and relatively fixed increase in prothrombic activity occurs in sera from platelet-free normal plasma, from hemophilic blood or plasmas and in stored normal and hemophilic blood. In none of these sera or plasmas is more than a very small quantity of prothrombin consumed; therefore, nearly all of the prothrombin remains. This, however, does not account for the striking increase in prothrombic activity. The most direct and simplest explanation is that an actual increase in prothrombin occurs. For this to happen one may postulate that plasma contains an inactive or precursor form of prothrombin. Bordet (10) developed the hypothesis that all prothrombin (serozyme) in circulating blood is in an inactive form. Quick and Stefanini (9) concluded that in human plasma part of the prothrombin is active, but a much greater proportion is in the precursor state. This inactive prothrombin, like active prothrombin, is completely adsorbed and eluted. The eluate in contact with glass likewise increases markedly in prothrombic activity, presumably because the precursor is gradually changed to active prothrombin. Recently it was found that the quantity of thromboplastin required for maximum prothrombic activity varies with the prothrombin concentration (11). When the prothrombin is reduced by means of Dicumarol or vitamin K deficiency, the thromboplastin requirement decreases. Considerably more thromboplastin is needed to obtain the minimum prothrombin time of stored plasma than of fresh plasma, which suggests that an increase of prothrombin itself occurs.

If the increase in prothrombic activity is not due to an increase of active prothrombin, then it becomes necessary to postulate that an accelerator is generated to account for the decrease of the prothrombin time from the normal of 12 seconds to eight seconds. Alexander and his associates (12) have attempted to establish that such a specific agent exists. They have named it spca (serum prothrombin converting accelerator) because they maintain that the prothrombic activity of serum is due largely to the evolution of this factor during clotting. If their contentions are correct, then the marked increase of prothrombic activity found in the serum from hemophilic or from thrombocytopenic blood should be due to spca, but according to their findings this factor is low in these sera (13, 14). From this it would follow that the marked hyperprothrombic activity in these sera is not due to the evolution of an accelerator but to an actual increase in prothrombin.

According to Alexander, spca, like prothrombin, is adsorbed by $BaSO_4$ and eluted with sodium citrate. In isolating spca, they allow blood to clot and treat the serum with $BaSO_4$ (20 mgm. per 1 cc. serum). From their statement (15): "most of the prothrombic activity was in the supernatant" after adsorption with $BaSO_4$, one must infer that these investigators assume that differential adsorption occurs in which spca is separated from prothrombin. On repeating their procedure, it has been found that as much as two-thirds of the prothrombic activity of serum is removed by 20 mgm. of $BaSO_4$ per 1 cc. (16). There is therefore a strong probability that the separation of spca and prothrombin is more apparent than real and that the product considered to be the accelerator contains an undetermined amount of prothrombin. Alexander and Landwehr's (17) finding that the evolution of spca during storage is small in various hypoprothrombic states might well be explained by a low concentration of prothrombin in the accelerator preparation. To determine how much of the activity is due to prothrombin and how much to an accelerator becomes not only a formidable but a speculative problem.

Thus, while the possibility of an accelerator factor should not be ignored, it seems simpler and

perhaps more firmly supported by experimental evidence that the hyperprothrombic activity in the conditions discussed is due to an actual increase in active prothrombin. The statement of Stefanini and Crosby (18) that the prothrombin time of serum is not influenced by the activation of the precursor of prothrombin in less than two hours after the completion of clotting is not in accord with the findings of the writers. In the clotting of native human plasma the prothrombin time of the serum attains a constant value in about 15 minutes after all the fibrinogen has been converted to fibrin. In oxalated plasma, the conversion of inactive prothrombin to the active state is slow. At 4° C. the reaction usually requires more than 24 hours to go to completion, even in contact with a glass surface, and in a silicone-coated container it even takes considerably longer. This permits the removal of both prothrombin and prothrombinogen from oxalated plasma by adsorption with tricalcium phosphate, and the subsequent recovery of both forms by elution with sodium citrate.

The finding that neither storage nor the clotting of platelet-poor dog plasma causes an increase of prothrombic activity such as is observed in human plasma, makes it unlikely that dog blood contains a prothrombin converting factor of the type of spca. One is at a loss, therefore, to find a better explanation for the high prothrombic activity of dog blood than that it contains a much higher concentration of active prothrombin than does human blood, but has little or no inactive prothrombin.

SUMMARY

The comparative prothrombic activity of dog and human blood were studied by means of the one-stage prothrombin test, the prothrombin consumption test and the adsorption and elution technique for determining prothrombin.

It was found that the prothrombic activity of dog blood is much greater than that of human blood. When oxalated dog plasma is stored, the prothrombin time is increased due to loss of labile factor. When the latter is restored, the prothrombin time returns to the value obtained for fresh plasma. The serum from platelet-poor normal plasma has a prothrombin time only slightly less than that of plasma.

Human plasma on storage likewise shows a progressive decrease of prothrombic activity but when the labile factor is restored, the prothrombin time becomes shorter than that of the fresh plasma. A similar increase in prothrombic activity is found when normal platelet-poor plasma, or hemophilic plasma clots.

Possible explanations for these findings are discussed. It is concluded that dog blood contains a high concentrate of free or active prothrombin but little or no inactive prothrombin, whereas human plasma has a much smaller amount of free prothrombin, but a high concentration of inactive prothrombin (prothrombinogen), which in contact with a glass surface becomes converted to the active state.

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THE EFFECT OF THE CHRONIC ADMINISTRATION OF ADRENAL MEDULLARY HORMONES TO MAN ON ADRENOCORTICAL FUNCTION AND THE RENAL EXCRETION OF ELECTROLYTES

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The acute and chronic administration of adrenaline to experimental animals and its acute administration to man have been shown to increase adrenocortical activity.

In 1908 Babes and Jonesco reported that repeated injections of adrenaline caused adrenocortical hypertrophy in rabbits (1). Vogt found by direct assay of adrenal venous blood of dogs and cats that there was an increased output of adrenocortical hormone following the injection of adrenaline (2). She subsequently reported that multiple injections of adrenaline produced adrenal hypertrophy in intact but not in hypophysectomized rats (3).

Long and Fry described a decrease in adrenocortical cholesterol and ascorbic acid following the injection of adrenaline in intact but not in hypophysectomized rats (4). This and subsequent work by Gershberg and associates (5) indicate that adrenaline causes an increased output of adrenocorticotrophin.

Using a decrease in the level of circulating eosinophils as a very sensitive measure of increased adrenocortical activity, Recant and colleagues showed that a single dose of adrenaline increases adrenocortical activity in the dog, rat, and man (6). Although they found eosinopenia in men receiving multiple injections of adrenaline over periods as long as 48 hours, there was no evidence of increased adrenocortical activity as measured by the urinary excretion of steroids and uric acid. However, Bliss, Rubin, and Gilbert (7) reported increases in urinary uric acid and 17-ketosteroids in normal men and women given 8 mg. of adrenaline in oil in a period of 12 hours.

Guest and coworkers showed that sustained eosinopenia does not occur uniformly in patients given repeated injections of adrenaline (8).

Adrenaline prepared from biological material contains about 85 per cent epinephrine and 15 per cent nor-epinephrine (9) unless a special process is included to remove nor-epinephrine. The adrenaline used in the present study was manufactured from biological material and did contain nor-epinephrine. Since nor-epinephrine produces little or no eosinopenia (10, 11), the increased adrenocortical function which follows the administration of adrenaline must be due primarily to its epinephrine content. However, some of the results reported in the present paper may well have been due to nor-epinephrine. The designation adrenaline is used in this communication to indicate a mixture of epinephrine and nor-epinephrine.

The observations reported were undertaken to determine what manifestations of increased adrenocortical activity occur during the chronic administration of adrenaline to man. To this end the level of circulating eosinophils, the urinary excretion of uric acid, the urinary excretion of steroids, and the metabolism of nitrogen, sodium, chloride, potassium, phosphorus, and calcium have been studied in men receiving repeated injections of adrenaline over a period of days.

Among the effects observed have been increased urinary excretion of sodium, chloride, calcium, and uric acid, and decreased urinary excretion of potassium. The changes in the urinary excretion of sodium, potassium, and chloride are opposite to those seen with increased adrenocortical activity. These changes in urinary excretion are of interest in connection with previous demonstrations in experimental animals that although adrenaline in large dosage causes oliguria, adrenaline in smaller amounts produces diuresis of water and chloride (12–16).

Increased excretion of sodium and chloride and diminished excretion of potassium were observed by Bliss, Rubin and Gilbert in a patient with rheumatoid arthritis given 8 mg. of adrenaline in oil per day for three days (7).

EXPERIMENTAL METHODS

Chemical methods. The subjects lived on a metabolic ward during the study. Food was prepared in a kitchen used only for this purpose. Aliquots of diet and feces were obtained by the "wet method" described by Reifenstein, Albright and Wells (17). Dietary, urinary, and fecal nitrogen were done by a macro-Kjeldahl method (18) and plasma protein and non-protein nitrogen by a micro-Kjeldahl method (18). Phosphorus was determined by the method of Fiske and Subbarow (19), calcium according to Fiske and Logan (20), creatinine as described by Peters (21), glucose by the method of Nelson (22), and chloride as described by Van Slyke (23). Uric acid was done by Archibald's modification of the method of Kern and Stransky as described by Forsham and associates (24). Sodium and potassium were determined on a Beckman flame photometer. Sodium determinations were done first and the potassium standards and samples for analysis of potassium brought to the highest concentration of sodium present in the samples. The hematocrit, CO_2 content, and pH of blood were determined by the technique of Shock and Hastings (25). From these data the bicarbonate content of plasma was calculated. Eosinophil counts were done by Forsham's modification of the method of Dungar (24). In the cases of R. K. and B. R., urinary steroids were determined in Dr. Dobriner's laboratory.

Formaldehydogenic and 17-ketosteroids were determined after an extraction procedure described by Lieberman and Dobriner (26). The values reported are the sum of the values in the three fractions described in this procedure. Formaldehydogenic steroids were determined on these fractions by a procedure essentially that of Corcoran and Page (27).

On the other subjects 17-ketosteroids were done by the method of Callow as modified by Talbot and colleagues (28, 29) and formaldehydogenic steroids by the method of Corcoran and Page[1] (27).

Subjects. R. K. was a 31-year-old Negro. Although a childhood disease, presumably poliomyelitis, had resulted in atrophy of some muscle groups in the lower extremities, he did not require artificial support in walking. General health had been excellent and no abnormalities were found on physical examination. Hematological data and the results of urine and stool examination were normal. C_{IN} was 85 cc., C_{PAH}, 397 cc. and Tm_G, 260 mg. per minute per 1.73 sq. m.[2] The cause of these low values was not apparent. There was no history of renal disease and urinalysis and intravenous and retrograde pyelograms were normal. Following 0.4 mg. of adrenaline subcutaneously there was a 64 per cent fall in the concentration of circulating eosinophils. Fifteen days before the start of the present study he completed a period of 12 days of administration of 100 mg. of ACTH per day. His response to that agent was normal.

B. R. was a 32-year-old white man admitted because of balanitis due to a beta hemolytic streptococcus. This infection cleared promptly during treatment with sulfadiazine. General health had been good, no abnormalities were found on physical examination, and hematological data and the results of urine and stool analyses were normal. C_{IN} was 129 cc., C_{PAH}, 896 cc., and Tm_G, 386 mg. per minute per 1.73 sq. m. Following 0.4 mg. of adrenaline subcutaneously there was a 54 per cent fall in the concentration of circulating eosinophils. Fifteen days before the start of the present study he completed a period of 12 days of administration of 100 mg. of ACTH per day. His response to that agent was normal.

T. B. was a 67-year-old white man whose general health had been excellent. No abnormalities were found on physical examination, urinalysis, and hematological and stool examination. C_{IN} was 79 cc., Tm_{PAH} 78 mg., and Tm_G 243 mg. per minute per 1.73 sq. m. These are normal values for his age group. Following 0.3 mg. of adrenaline subcutaneously there was a 47 per cent fall in circulating eosinophils, a normal response for his age group.

G. K., a 42-year-old Negro, whose general health had been good, had a herniorrhaphy a month prior to this study. The only physical abnormality found on examination was a moderately intense short rough apical systolic murmur. Hematological data and the results of stool examination and urinalysis were normal except for the presence of five to 10 leukocytes per high power field in the urinary sediment. Teleoroentgenogram of the chest and electrocardiogram were normal. C_{IN} was 111 cc. and Tm_G, 341 mg. per minute per 1.73 sq. m. There was a 71 per cent fall in eosinophil concentration after 0.3 mg. of adrenaline subcutaneously.

Experimental procedure. After a period of equilibration, R. K. and B. R. were studied during a three-day control period, a three-day period of administration of 0.4 mg. of adrenaline in saline subcutaneously every four hours, a three-day period of administration of 1 mg. of adrenaline in peanut oil intramuscularly every four hours, and a six-day recovery period. After a period of adjustment to the diet, G. K. was studied during a six-day control period, a three-day period of administration of

[1] We are indebted to Dr. F. E. Houghton, Ciba Pharmaceutical Products, Inc., for the supply of desoxycorticosterone used in this method.

[2] Glomerular filtration rate (C_{IN}), effective renal plasma flow (C_{PAH}), maximal tubular excretory rate of sodium p-aminohippurate (Tm_{PAH}), and maximal rate of tubular glucose reabsorption (Tm_G) were determined by methods described elsewhere (30).

peanut oil[3] alone intramuscularly every four hours, a second three-day control period, a three-day period of administration of 1 mg. of adrenaline in peanut oil intramuscularly every four hours, and a three-day recovery period.

The periods for T. B. were the same except that the period of administration of adrenaline in oil lasted six days during the last three of which 1.5 mg. of adrenaline was given every four hours, and that the recovery period lasted four days.

The blood pressure, recorded as the mean of seven consecutive readings, and the pulse rate were determined every morning at 7:45 a.m. before the subjects arose. Fasting blood samples were drawn just before the urine collections for the day were completed at 8:00 a.m. Injections of adrenaline were started at 9:00 a.m. Thus, the fasting blood samples were drawn three hours after the 5:00 a.m. injection of adrenaline. In two subjects blood for eosinophil counts was also drawn at 1:00 p.m., four hours after the preceding injection of adrenaline.

The daily urinary excretions of sodium, potassium, chloride, nitrogen, calcium, phosphorus, uric acid, creatinine, glucose, 17-ketosteroids, and formaldehydogenic steroids were determined for all subjects and in the cases of R. K. and B. R., fecal sodium, potassium, chloride, nitrogen, calcium, and phosphorus were also estimated. Serum sodium, potassium, chloride, calcium, phosphorus, pH, bicarbonate content, non-protein nitrogen, protein, uric acid, and glucose, and blood eosinophil counts were determined at appropriate intervals.

The daily dietary intakes for G. K. and T. B. were water 2800 cc., sodium 91 meq., potassium 89 meq., chloride 84 meq., calcium 269 mg., phosphorus 1228 mg., and nitrogen 16.1 gm.; for R. K., water 2800 cc., sodium 96 meq., chloride 90 meq., potassium 71 meq., calcium 260 mg., phosphorus 1163 mg., and nitrogen 16.0 gm.; and for B. R., water 2800 cc., sodium 96 meq., chloride 91 meq., potassium 78 meq., calcium 273 mg., phosphorus 1182 mg., and nitrogen 16.1 gm.

[3] Both the adrenaline in peanut oil and the oil alone to serve as a control were supplied through the courtesy of Dr. E. A. Sharpe of Parke, Davis, and Company. The adrenaline was manufactured before this company introduced a process to remove nor-epinephrine.

RESULTS

The data on functions affected by the administration of adrenaline are recorded in Tables I through IV. In no instance were any alterations in function observed during the administration of peanut oil alone.

On the first day of administration of adrenaline there was in every case a decrease in the concentration of eosinophils in the peripheral blood four

TABLE I

Daily metabolic data on subject R. K.†*

Period	Wt. of Pt.	Urine vol.	Sodium		Chloride		Potassium		Calcium	Uric acid	Urinary steroids		Blood eosinophils
			Urine	Bal.	Urine	Bal.	Urine	Bal.	Urine	Urine	17-ketosteroids	Formaldehydogenic steroids	
	kg.	*cc.*	*meq.*	*meq.*	*meq.*	*meq.*	*meq.*	*meq.*	*mg.*	*gm.*	*mg.*	*mg.*	*cells/cu. mm.*
Control	68.1	1990	82	+ 5	81	+ 2	41	+ 2	118	.59	16	0.2	—
	68.0	1470	95	− 8	87	− 4	44	− 1	124	.59	16	0.2	67
	68.1	1700	84	+ 3	81	+ 2	44	− 1	116	.59	16	0.2	—
Adrenaline in saline *2.4 mg./day*	68.2	1960	111	−28	85	− 4	32	+ 9	163	.80	15	0.4	103
	67.7	1380	78	+ 5	66	+15	28	+13	154	.70	15	0.4	55
	68.4	1260	68	+15	64	+17	32	+ 9	151	.69	15	0.4	64
Adrenaline in oil *6 mg./day*	68.2	1380	115	−32	105	−24	30	+11	193	.92	17	0.5	55
	67.4	1580	123	−40	112	−31	30	+11	165	.86	17	0.5	58
	67.2	1250	102	−19	99	−18	40	+ 1	164	.69	17	0.5	33
Recovery	67.2	1150	40	+47	52	+31	52	−12	110	.58	13	0.6	55
	67.6	960	11	+76	27	+56	50	−10	82	.69	13	0.6	—
	67.9	1200	11	+76	30	+53	54	−14	84	.68	13	0.6	74
	68.4	1420	29	+58	32	+51	44	− 4	85	.73	14	0.7	72
	68.4	1160	46	+41	43	+40	38	+ 2	86	.67	14	0.7	—
	68.8	1620	83	+ 4	68	+15	39	+ 1	103	.69	14	0.7	—
	68.6												66

* The balances shown in this and subsequent tables are adjusted for the apparent positive balances of the control period which were of the magnitude usually observed and probably due largely to cutaneous losses. These adjusted balances are the deviations of the daily balances from the average daily balances of the control period.

† Daily intake was: water, 2800 cc., Na, 96 meq., Cl, 90 meq., K, 71 meq., and Ca, 260 mg.

TABLE II

*Daily metabolic data on subject B. R.**

Period	Wt. of Pt.	Urine vol.	Sodium		Chloride		Potassium		Calcium	Uric acid	Urinary steroids		Blood eosinophils
			Urine	Bal.	Urine	Bal.	Urine	Bal.	Urine	Urine	17-ketosteroids	Formaldehydogenic steroids	
	kg.	*cc.*	*meq.*	*meq.*	*meq.*	*meq.*	*meq.*	*meq.*	*mg.*	*gm.*	*mg.*	*mg.*	*cells/cu. mm.*
Control	50.9	1680	82	− 2	87	− 7	54	− 1	112	.88	21	0.1	—
	51.0	2140	85	− 5	80	0	53	0	120	.88	21	0.1	—
	50.7	1670	74	+ 6	73	+ 7	53	0	117	.88	21	0.1	111
Adrenaline in saline *2.4 mg./day*	50.9	1490	74	+ 7	61	+19	29	+26	159	.86	22	0.1	134
	51.1	1810	90	− 9	81	− 1	37	+18	173	.92	22	0.1	70
	51.1	1640	98	−17	92	−12	43	+12	162	.93	22	0.1	77
Adrenaline in oil *6 mg./day*	51.1	2230	140	−59	124	−44	48	+ 7	215	.95	21	1.1	106
	50.6	1890	97	−16	97	−17	46	+ 9	174	.90	21	1.1	70
	50.5	2320	90	− 9	92	−12	69	−14	145	.94	21	1.1	64
Recovery	50.2	1250	20	+60	45	+35	78	−24	68	.83	19	0.5	70
	50.6	1330	8	+72	24	+56	54	0	66	.68	19	0.5	—
	50.9	1110	22	+58	35	+45	73	−19	88	.86	19	0.5	72
	51.6	1480	32	+48	36	+44	43	+11	85	.75	20	1.2	61
	51.8	1410	52	+28	53	+27	50	+ 4	111	.84	20	1.2	—
	51.7	1800	57	+23	62	+18	50	+ 4	111	.82	20	1.2	—
	51.8												66

* Daily intake was: water, 2800 cc., Na, 96 meq., Cl, 91 meq., K, 78 meq., and Ca, 273 mg.

TABLE III

*Daily metabolic data on subject G. K.**

Period	Wt. of Pt.	Urine vol.	Sodium		Chloride		Potassium		Calcium	Uric acid	Urinary steroids		Blood eosinophils
			Urine	Bal.	Urine	Bal.	Urine	Bal.	Urine	Urine	17-ketosteroids	Formaldehydogenic steroids	
	kg.	*cc.*	*meq.*	*meq.*	*meq.*	*meq.*	*meq.*	*meq.*	*mg.*	*gm.*	*mg.*	*mg.*	*cells/cu. mm.*
Control	61.2	1860	68	+14	62	+12	60	+ 5	39	.86	9	1.0	—
	61.6	2060	77	+ 5	70	+ 4	68	− 3	35	.86	9	1.0	—
	61.6	2200	82	0	75	− 1	66	− 1	35	.79	9	1.0	—
	61.6	2070	86	− 4	84	−10	72	− 7	40	.79	10	1.0	—
	61.6	2330	93	−11	79	− 5	65	0	40	.76	10	1.0	—
	61.5	2100	87	− 5	77	− 3	62	+ 3	33	.74	10	1.0	465
Oil	61.1	1720	93	−11	83	− 9	71	− 6	41	.76	10	0.8	417
	61.5	2290	72	+10	75	− 1	74	− 9	42	.73	10	0.8	456
	61.4	1830	70	+12	66	+ 8	71	− 6	44	.71	10	0.8	498
Control	61.4	1880	79	+ 3	69	+ 5	65	0	37	.74	9	0.7	470
	61.4	2070	81	+ 1	76	− 2	73	− 8	48	.78	9	0.7	—
	61.2	2030	81	+ 1	73	+ 1	67	− 2	51	.75	9	0.7	—
Adrenaline in oil *6 mg./day*	61.5	2380	107	−25	66	+ 8	47	+18	89	.85	6	0.9	454
	61.0	2450	137	−55	110	−36	65	0	70	.82	6	0.9	419
	60.9	2250	132	−50	132	−58	72	− 7	67	.80	6	0.9	600
Recovery	60.4	1760	87	− 5	103	−29	94	−29	40	.73	8	0.8	537
	60.7	1750	47	+35	53	+21	70	− 5	45	.76	8	0.8	355
	60.7	1750	40	+42	42	+32	73	− 8	43	.71	8	0.8	294
	61.2												412

* Daily intake was: water, 2800 cc., Na, 91 meq., Cl, 84 meq., K, 89 meq., and Ca, 269 mg.

TABLE IV

*Daily metabolic data on subject T. B.**

Period	Wt. of Pt.	Urine vol.	Sodium		Chloride		Potassium		Calcium	Uric acid	Urinary steroids		Blood eosinophils
			Urine	Bal.	Urine	Bal.	Urine	Bal.	Urine	Urine	17-ketosteroids	Formaldehydogenic steroids	
	kg.	*cc.*	*meq.*	*meq.*	*meq.*	*meq.*	*meq.*	*meq.*	*mg.*	*gm.*	*mg.*	*mg.*	*cells/cu. mm.*
Control	80.0	1770	69	+ 9	64	+ 4	68	+ 1	100	.56	5	1.0	—
	80.0	1710	64	+14	59	+ 9	62	+ 7	88	.80	5	1.0	—
	80.1	1960	84	− 6	70	− 2	72	− 3	104	.87	5	1.0	—
	80.1	1790	83	− 5	73	− 5	71	− 2	80	.84	6	0.7	—
	80.1	2210	96	−18	80	−12	77	− 8	91	.83	6	0.7	—
	80.1	1810	72	+ 6	62	+ 6	67	+ 2	103	.83	6	0.7	409
Oil	80.0	2020	75	+ 3	68	0	70	− 1	108	.85	6	1.0	310
	80.0	1930	84	− 6	76	− 8	72	− 3	109	.84	6	1.0	346
	80.0	1530	70	+ 8	66	+ 2	70	− 1	98	.82	6	1.0	483
Control	80.1	2220	91	−13	80	−12	78	− 9	116	.81	6	0.7	450
	80.0	1620	80	− 2	73	− 5	73	− 4	95	.75	6	0.7	—
	79.9	1550	64	+14	66	+ 2	69	0	100	.79	6	0.7	—
Adrenaline in oil *6 mg./day*	79.9	2040	88	−10	68	0	49	+20	140	.85	6	0.8	340
	79.4	1770	98	−20	74	− 6	46	+23	136	.95	6	0.8	230
	79.4	1560	87	− 9	77	− 9	52	+17	129	.78	6	0.8	334
Adrenaline in oil *9 mg./day*	79.7	1220	82	− 4	71	− 3	59	+10	136	1.23	6	0.8	537
	79.4	1490	85	− 7	78	−10	64	+ 5	139	.90	6	0.8	640
	79.3	1680	90	−12	78	−10	72	− 3	125	.71	6	0.8	577
Recovery	79.4	1040	42	+36	58	+10	86	−17	75	.65	5	0.8	415
	79.6	1300	44	+34	55	+13	85	−16	93	.67	5	0.8	593
	79.6	1170	61	+17	65	+ 3	80	−11	98	.83	5	0.8	583
	79.6	1270	82	− 4	81	−13	69	0	111	.74	5	0.8	394
	79.9												

* Daily intake was: water, 2800 cc., Na, 91 meq., Cl, 84 meq., K, 89 meq., and Ca, 269 mg.

hours after the first injection of adrenaline. In subjects R. K. and B. R., the level of circulating eosinophils at 8:00 a.m., three hours after the preceding injection of adrenaline, was moderately decreased throughout the entire period of administration of adrenaline. After the withdrawal of adrenaline, the eosinophil concentration rose toward the control values in R. K., but not in B. R. In the other two subjects, although there was a fall in the concentration of eosinophils following the first injection of adrenaline, the values during the latter part of the period were actually higher than the control values. The 1:00 p.m. levels of circulating eosinophils determined only in R. K. and B. R. approximated the 8:00 a.m. values.

During the administration of adrenaline there was no change in 17-ketosteroid excretion. During and following adrenaline, R. K. and B. R. showed slightly increased formaldehydogenic steroid excretion. Even if these changes are regarded as significant they indicate no more than a mild degree of adrenocortical stimulation. The other two subjects showed no change in formaldehydogenic steroid excretion.

The urinary uric acid was slightly increased during the entire period of administration of adrenaline and returned to the control values after withdrawal of adrenaline. There was no consistent change in plasma uric acid.

The average increase in plasma glucose during the administration of adrenaline was 15 mg. per 100 cc. During this period the average increase in urinary glucose excretion was 1.2 gm. per day.

There were no consistent changes in the fecal excretions of the elements studied in the two cases in which stool analyses were done. Adjusted balances for sodium, potassium, and chloride are recorded in Tables I through IV. Unadjusted balances during the control period were positive. These positive balances were of the magnitude

usually observed in control periods and probably due to cutaneous losses. The average daily positive balance of the control period was assumed to represent cutaneous loss and was subtracted from the observed balance for each day. In the two cases in which fecal determinations were not made, fecal excretions were also assumed to be constant. The adjustment in these two cases includes fecal excretion as well as cutaneous loss. Balances derived in this way are referred to as adjusted balances.

No consistent change in the urinary excretion of sodium and chloride occurred during the administration of adrenaline in saline. During the administration of adrenaline in oil, there was an increase in the urinary excretion and concentration of these ions. The subjects were thus in negative sodium and chloride balance during the administration of adrenaline in oil. Subsequently the urinary excretions and concentrations of sodium and chloride fell, and the subjects retained sodium and chloride. There were no consistent changes in the serum concentrations of sodium and chloride.

The changes in the urinary excretion of potassium were in the opposite direction to those of sodium and chloride. There was a decrease in the urinary excretion and concentration of potassium during the administration of adrenaline whether in saline or oil. During the recovery period the urinary excretion and concentration rose. Thus, there were positive balances of potassium during the administration of adrenaline followed by compensatory negative balances in the recovery period. There were no consistent changes in the serum potassium levels.

The urinary calcium excretion and concentration were increased during the entire period of administration of adrenaline and fell to values below the control levels after withdrawal of adrenaline.

There were no consistent changes in the urinary excretion of nitrogen and phosphorus.

The changes in urinary volume were small. In the case of B. R. and G. K., there was an increase in urinary volume during the administration of adrenaline and a diminution in urinary volume in the recovery period. R. K. and T. B. showed no definite change in urinary volume. Because of variations in extrarenal losses of water, changes of this magnitude are of little value in estimating water balance. However, during adrenaline administration all the subjects lost weight which they regained in the recovery period. The losses and subsequent gains were for R. K., 1.0 and 1.4 kg., for B. R., 0.9 and 1.6 kg., for T. B., 0.5 and 0.5 kg., and for G. K., 1.1 and 0.8 kg. These changes in weight may have been due to changes in body water. If so, then all subjects may be said to have had a larger urinary volume than they would have had with the same extrarenal loss of water if adrenaline had not been given.

The plasma protein concentration increased slightly in every case during the administration of adrenaline in oil. The average increase was 0.4 gm. per 100 cc. There were no consistent changes in creatinine excretion, urinary pH, the hematocrit, nor in the serum non-protein nitrogen, phosphorus, bicarbonate, or pH.

The average increase in the 8:00 a.m. pulse rate during the administration of adrenaline in oil was three beats per minute, and in the pulse rate an hour after the 9:00 a.m. injection, three beats per minute over the control value an hour after the administration of oil alone. The average changes in the 8:00 a.m. systolic and diastolic blood pressures were + 2 and − 2 mm. of mercury respectively, and in the systolic and diastolic pressures an hour after the 9:00 a.m. injection of adrenaline in oil, + 12 and 0 mm. of mercury over the control values an hour after the administration of oil alone.

DISCUSSION

The only evidence suggestive of increased adrenocortical activity during the administration of adrenaline was the decrease in the level of circulating eosinophils in B. R. and R. K., and the small changes in the formaldehydogenic steroid excretion in these two subjects. The other subjects showed no changes suggestive of altered adrenocortical activity. It is apparent that adrenaline in the time-dosage schedule used in this study is no more than a very weak chronic stimulus to adrenocortical activity.

The changes in the excretion of electrolytes during the administration of adrenaline indicate that renal function was modified by some mechanism other than adrenocortical stimulation. In view of this, the increased urinary excretion of uric acid cannot be considered a valid measure of adrenocor-

tical activity since this may have been due to renal effects not caused by an adrenocortical hormone.

During the administration of adrenaline in oil there was increased renal excretion of sodium, chloride, and calcium, retention of potassium, and loss of weight. The failure of adrenaline in saline to produce all these changes is presumably due to the smaller dose of epinephrine employed or to its more transitory action. The changes in weight suggest that there was greater renal excretion of water than would have occurred with the same extrarenal loss of water if adrenaline had not been given.

Diuresis of water and chloride has been observed in acute experiments in animals given relatively small amounts of adrenaline (12–16). Although the effect of adrenaline on the renal excretion of sodium, calcium, and potassium was not studied in the animal experiments, it appears probable that the same processes were affected in those experiments as in the one reported here. There is no direct evidence as to the mechanism of the alterations in renal excretion of electrolytes and water, though naturally it has been suggested that they are due to a direct effect of adrenaline on the kidney, altering either glomerular filtration or tubular function (15). An alteration in tubular function is compatible with our data and suggested by the fact that the changes in renal excretion of electrolytes were not all in the same direction, potassium excretion being diminished while sodium, chloride, and calcium excretion were increased. It is also compatible with the observation of Chasis and associates (31) that the subcutaneous injection of 1 mg. of adrenaline does not alter glomerular filtration rate in man. The conditions of their experiments did not permit the study of the effect of adrenaline on urinary volume.

The concept that the effect of adrenaline on renal excretion is a direct effect of adrenaline on the kidney rather than the result of changes produced elsewhere in the body is supported by the observation of Richards and Plant (32) that perfusion of the kidney *in situ* produces diuresis and the observation of Winton (33) that adrenaline produces diuresis in the heart-lung-kidney preparation.

Although the diuresis observed in animal experimentation has been generally attributed to the epinephrine content of adrenaline, Horres, Eversole and Rock have recently presented evidence that it is caused by nor-epinephrine and not by epinephrine (16).

SUMMARY AND CONCLUSIONS

Certain metabolic effects of the chronic administration of adrenal medullary hormones to men are reported.

Adrenal medullary hormones in the time-dose schedule employed are no more than a very weak chronic stimulus to adrenocortical activity.

Under the conditions of this study, the chronic administration of adrenal medullary hormones caused increased urinary excretion of sodium, chloride, calcium, and uric acid, and diminished urinary excretion of potassium.

ACKNOWLEDGMENTS

We are indebted to Dr. Konrad Dobriner in whose laboratory at the Sloan-Kettering Institute certain of the steroid determinations were done; to Dr. Roger K. McDonald and Dr. John H. Miller for renal function determinations; to Mr. Marvin J. Yiengst for serum bicarbonate and pH determinations; and to Eloise Bright, Mary Jane Ford, Stewart Humphreys, James Laster, John Melvin, Janis Parsons, Mildred Salchunas, Patricia Skinner, and Millard Starnes for technical assistance.

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THE EFFECT OF HIGH SPINAL ANESTHESIA ON THE RENAL HEMODYNAMICS AND THE EXCRETION OF ELECTROLYTES DURING OSMOTIC DIURESIS IN THE HYDROPENIC NORMAL PREGNANT WOMAN [1]

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In previous papers (1, 2) it was demonstrated that the normal pregnant woman subjected to autonomic blockade with high spinal anesthesia develops a marked fall in blood pressure leading to a shock-like state.

Since the blood flow to the kidneys constitutes approximately one quarter of the total cardiac output under resting conditions, it seemed that a study of the renal hemodynamics under high spinal anesthesia might afford the opportunity of examining the response of an important part of the vascular bed to this procedure.

Concurrently with the study of renal hemodynamics it was considered of some interest to extend the observations to the excretion of sodium, chloride and potassium. The relationship between renal hemodynamics and electrolyte excretion is at present controversial, and it was thought likely that additional information regarding this relationship might be derived from the present study.

In order to examine the response of the kidneys to this type of autonomic blockade, it was necessary to use a technique which would be applicable to a period of study of short duration. Thus the immediate response to spinal anesthesia could be followed and observations continued until the blood pressure had almost returned to levels preceding the injection of the spinal anesthetic. Previous studies (3–5) employing osmotic diuresis with hypertonic mannitol solution in hydropenia, had shown that this technique was applicable to a short period of study and that results could be obtained which varied little from individual to individual. Under these conditions sufficiently large urine flows could be obtained in ten minutes to reduce the errors in urine collection and the effects of time lag due to dead space. It should be pointed out, however, that even with this technique such errors cannot be entirely avoided and the results may not accurately reflect short time changes in kidney function. Our own experience (6) with pregnant women before and during high spinal blockade had indicated that the use of water diuresis was not advisable since under these conditions the urine flow is variable and often reaches low volumes insufficient to perform accurate clearances. This was in accord with previous observations in animal and man that water diuresis is inhibited by emotional stress or by afferent stimuli evoked merely by the insertion of a needle into the spinal canal (7–11).

Osmotic diuresis with hypertonic mannitol in hydropenia also had several other advantages to offer. The water-conserving capacity of the kidney of the hydropenic individual could be studied both prior to induction of diuresis and following loading, using the standards of comparison which are defined by the flow-load relationship (3, 5). The excretion of sodium and chloride had been shown to vary little throughout this procedure, the concentrations of these two ions in the urine remaining remarkably constant. It would thus be possible to obtain a baseline of renal function which would be consistent from one patient to another. Variations from this pattern brought about by spinal anesthesia would then be readily detectable.

MATERIAL AND METHOD

The material consisted of five normotensive subjects whose ages varied from 20 to 30 years and who were in

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the last trimester of pregnancy. All had been followed in the prenatal clinic and none had any history of toxemia or renal or hypertensive disease. The patients were admitted to the hospital and kept at bed rest for a few days before the experiment. At 4 p.m. on the day prior to the test, the patients received a dry meal consisting of peanut butter, crackers and raisins. The patients were instructed not to ingest water or food until the next day after the test had ended. At 8 a.m. of the day of the procedure, a spinal anesthesia catheter was introduced into the subarachnoid space, following the technique described elsewhere (1). Thereafter, a multi-eyed Foley catheter was introduced and left in the bladder which was then completely emptied and the urine discarded. A period of 30 minutes was allowed for the patients to relax and for a preliminary urine collection. At the mid-point of this period, a sample of venous blood was taken.

At zero time, which marked the end of the preliminary period, 25% mannitol solution [4] in amounts calculated to achieve a plasma level of 20 mOsm/L was injected. After the priming injection, which was given over a period of 10 to 12 minutes, the plasma level was maintained by continuous infusion at a rate approximately equal to its disappearance rate by means of a constant infusion machine. Para-aminohippurate (PAH) was included in both priming and maintenance solutions in quantities which would enable simultaneous measurement of renal plasma flow. The volume of distribution of mannitol was taken as 20% of the total body weight and its rate of disappearance calculated as 1.5% per minute. The corresponding figures for PAH were 40% and 2.5% per minute.

An equilibration period of 30 minutes was allowed. At the end of this and of each subsequent period complete urine collections were obtained by aspiration with a

[4] Acknowledgment is made to Sharp and Dohme for their generous supply of mannitol.

TABLE I

BP, UF, RPF, GFR, FF, osmotic activity and concentrations of Na, Cl and K during osmotic diuresis with mannitol *

All flows are calculated per 1.73 M^2 per minute

Period	Concurrent time *min.*	Mean BP *mm. Hg*	UF *cc.*	PAH clearance *cc.*	Mannitol clearance *cc.*	FF	Na *mEq/L*	Cl *mEq/L*	K *mEq/L*	Effective osmotic activity *mOsm/L*	Load *μOsm*
Patient: W. R.			*Weight: 62.4 Kg.*				*S. A.: 1.62 M²*			*Age: 30*	
Prelim.	−30 to 0	108/70	0.32				59	172	89	1452	464
0 to 10 iv. injection of 227 cc. 25% mannitol; 3.75 cc. 20% PAH 10 to 101 iv. injection of 25% mannitol at 3.41 cc./min.; 20% PAH at 0.09 cc./min.											
1	26 to 39	115/60	7.88	685	132	.19	49	35.6	7	629	4956
2	39 to 50	115/60	6.79	639	112	.18	53	38.0	7	553	3754
3	50 to 62	120/65	7.04	596	125	.21	54	40.0	7	569	4005
Injection of spinal anesthetic—8 cc. 0.2% procaine											
4	68 to 78	88/51	4.79	476	89	.19	31	24.0	16	617	2955
5	78 to 90	100/58	4.64	502	84	.17	21	18.4	21	632	2932
6	90 to 101	103/62	5.87	575	105	.18	33	26.4	19	601	3528
Patient: F. S.			*Weight: 57.7 Kg.*				*S. A.: 1.60 M²*			*Age: 27*	
Prelim.	−30 to 0	105/63	0.50				219	220.0	89	812	408
0 to 10 iv. injection of 231 cc. 25% mannitol; 3.5 cc. 20% PAH 10 to 100 iv. injection of 25% mannitol at 3.15 cc./min.; 20% PAH at 0.09 cc./min.											
1	26 to 38	116/66	6.67	867	133	.15	62	58.0	22	544	3628
2	38 to 48	116/66	6.89	804	130	.16	62	59.6	18	516	3555
3	48 to 60	116/60	6.66	767	105	.14	61	55.2	17	549	3656
Injection of spinal anesthetic—10 cc. 0.2% procaine											
4	66 to 78	103/52	4.70	517	72	.14	40	40.0	22	546	2566
5	78 to 88	105/57	5.79	565	75	.13	33	33.6	24	529	3063
6	88 to 100	115/73	8.46	868	120	.14	39	43.6	26	533	4509

TABLE I—*Continued*

Period	Concurrent time *min.*	Mean BP *mm. Hg*	UF *cc.*	PAH clearance *cc.*	Mannitol clearance *cc.*	FF	Na *mEq/L*	Cl *mEq/L*	K *mEq/L*	Effective osmotic activity *mOsm/L*	Load *μOsm*
Patient: M. G.		*Weight: 62.7 Kg.*			*S. A.: 1.66 M²*				*Age: 23*		
Prelim.	−30 to 0	105/68	0.73				112	109.6	41	552	403
0 to 10 iv. injection of 227 cc. 25% mannitol; 3.7 cc. 20% PAH 10 to 84 iv. injection of 25% mannitol at 3.34 cc./min.; 20% PAH at 0.09 cc./min.											
1	20 to 31	106/60	9.36	521	102	.20	62	55.6	8	457	4278
2	31 to 41	98/50	13.31	723	122	.17	62	57.2	9	440	5856
3	41 to 52	104/56	11.90	567	103	.18	63	58.8	9	446	5307
Injection of spinal anesthetic—8 cc. 1% procaine											
4	52 to 62	67/28	2.13	111	22	.20	58	54.4	10	445	948
5	62 to 74	53/21	3.71	320	40	.13	19	17.6	16	440	1632
6	74 to 84	80/44	7.53	421	73	.17	16	17.6	20	423	3185
Patient: J. S.		*Weight: 66.6 Kg.*			*S. A.: 1.66 M²*				*Age: 20*		
Prelim.	−30 to 0	112/66	0.31				265	222.0	35	874	271
0 to 10 iv. injection of 242 cc. 25% mannitol; 4.0 cc. 20% PAH 10 to 102 iv. injection of 25% mannitol at 3.63 cc./min.; 20% PAH at 0.1 cc./min.											
1	27 to 38	122/70	7.96	952	132	.14	50	37.6	10	563	4481
2	38 to 50	127/74	6.93	668	100	.15	57	42.4	8	571	3957
3	50 to 62	127/74	7.51	705	118	.17	56	44.0	8	562	4221
Injection of spinal anesthetic—6 cc. 1% procaine											
4	70 to 81	87/52	3.53	419	52	.12	37	29.6	12	600	2118
5	81 to 92	113/67	4.75	523	69	.13	18	19.2	19	610	2896
6	92 to 102	100/62	3.85	412	52	.13	16	15.6	19	588	2264
Patient: M. B.		*Weight: 77 Kg.*			*S. A.: 1.76 M²*				*Age: 27*		
Prelim.	−30 to 0	106/64	1.31				86	82.0		279	366
0 to 15 iv. injection of 280 cc. 25% mannitol; 4.2 cc. 20% PAH 15 to 92 iv. injection of 25% mannitol at 4.2 cc./min.; 20% PAH at 0.12 cc./min.											
1	26 to 37	120/66	7.15		56		47	47.2	10	273	1952
2	37 to 48	114/56	10.55		84		54	52.0	9	336	3545
3	48 to 60	116/62	11.63		94		52	48.0	8	343	3989
Injection of spinal anesthetic—8 cc. 0.2% procaine											
4	60 to 70	49/25	7.02		59		50	45.6	7	356	2499
5	70 to 81	101/58	3.13		44		39	30.8	10	430	1346
6	81 to 92	106/61	4.56		46		38	32.8	11	444	2025

* BP = blood pressure; mean is the arithmetic mean of several readings as mentioned in Method. UF = urine flow; RPF = renal plasma flow; GFR = glomerular filtration rate; FF = filtration fraction.

syringe connected to the catheter and by injecting air into the bladder. Each patient had six collection periods of 10 to 12 minutes' duration. At the midpoint of each period a blood sample was taken from the antecubital vein and transferred to a heparinized vial. Three periods served as pre-spinal controls and three followed induction of the spinal blockade. In three patients, J. S., W. R. and F. S., a period of six to eight minutes was allowed imme-

diately after the administration of spinal anesthesia, and the urine collected during this period was discarded. In the other two cases collections were started immediately after the injection of procaine. Blood pressure readings (sphygmomanometer) and pulse rate were taken every four to five minutes during the control periods and every half to one minute during the spinal anesthesia.

Three patients received high selective spinal anesthesia to levels of C^4 with 0.2% procaine solution according to the method described elsewhere (1). In the remaining two cases the anesthesia was achieved with 1% procaine solution and a complete motor paralysis to levels of T^2 was obtained.

Urine and plasma specimens were analyzed for their content of mannitol, PAH, Na, Cl and K, using methods previously described (3). Effective osmotic activity of each specimen of urine was determined by measurement of depression of the freezing point.

RESULTS

In Table I are presented the essential data on five subjects. In it are listed concurrent time, mean readings of systolic and diastolic blood pressure over the period, urine flow, mannitol and PAH clearances and filtration fraction. The data pertaining to electrolytes refer to the concentrations of Na, Cl and K in the urine. The effective osmotic activity of the urine and excreted load per minute are also given. The amount of loading solute (mannitol), its time of injection, and the rate of administration of the sustaining infusion are presented. The amounts of PAH included for measurement of renal plasma flow are also indicated.

Blood pressure and pulse rate. The response of the blood pressure and pulse rate to the spinal blockade followed the same pattern described in other papers (1, 2). It will be seen that the blood pressure dropped markedly during the first few periods following spinal anesthesia and began to return to control levels at the onset of the last period. The pulse rate showed similar variation. The side effects of the procedure were the same as listed in other papers (1, 2) except for thirst due to the hydropenic state.

Osmolarity and urine flow. The preliminary urine flows for W. R., F. S., and J. S. were 0.5 cc./min. or less with an effective osmotic activity of more than 800 mOsm/L, indicating that the period of dehydration of 16 hours prior to the beginning of the loading procedure had been adhered to. From Figure 1 it will be seen that these cases fit well on the flow-load curve as described previously (3) for normal hydropenic individuals and that this relationship between flow and load was not altered by induction of spinal anesthesia.

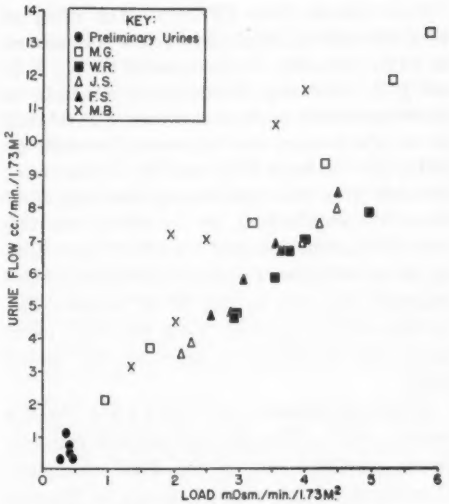

FIG. 1. URINE FLOW VS. EXCRETED LOAD

Two patients were not hydropenic at the onset of the observations. M.G., with a preliminary urine flow of 0.73 cc./min. and an initial osmolarity of 552 mOsm/L, became hydropenic only during the procedure. The points fell to the left of the curve during the initial post-loading periods, but as dehydration progressed during the induction of forced diuresis the points approached the normal curve. It seems likely that she ingested water during the period preceding the loading procedure. Case M. B. with an initial urine volume of 1.31 cc./min. and a total osmotic activity of 279 mOsm/L was certainly not hydropenic at the onset of the procedure nor did she begin to excrete urine with an osmolarity greater than that of plasma until period 2. The restriction of water was thus probably not rigidly enforced in M. G. and M. B. and this rendered difficult a consideration of their concentrating abilities. In all cases there was a marked drop in urine flow after induction of spinal anesthesia and a subsequent gradual rise to approximately control levels.

Renal plasma flow (RPF).[5] The effect of spinal blockade on renal plasma flow is consistent for all five subjects. In the cases of W. R., F. S. and J. S., following the autonomic blockade no observations were made on clearance of PAH until six to eight minutes after injection of procaine intrathecally. In cases M. G. and M. B. these measurements were made immediately following injection of the anesthetic agent. It will be seen that renal plasma flow sustained a marked drop following the introduction of procaine and that this effect gradually wore off, so that 30–40 minutes after injection of the anesthetic agent the PAH clearances were beginning to approach the control levels.

Glomerular filtration rate (GFR) and filtration fraction (FF). The effect of mannitol clearance closely paralleled that of the PAH clearances. Thus there was no marked change in filtration fraction during the procedure. There was a drop in GFR immediately following the autonomic blockade and a gradual return to control levels within 30–40 minutes.

Renal arterial resistance.[6] In addition to the observations already made it will be noted from Figures 2 and 3 that the renal arterial resistance both for J. S. and the mean values for the whole series was increased following spinal blockade.

Electrolytes. The excretions of Na and Cl paralleled each other. In the post-loading periods the urinary concentration of Na varied from 47 to 63 mEq/L and dropped in all cases following autonomic blockade. Unlike the hemodynamic changes, variations in Na concentration tended to become manifest only after a delay of several minutes after spinal blockade. The Cl concentrations in the urine likewise fell constantly after spinal anesthesia and the pattern of fall closely resembled that of the Na values. These values remained low despite the gradual rise of GFR. The concentrations of K rose after induction of spinal anesthesia in three subjects, but was not significantly altered in two. The minute loss of K was variable in the different subjects, being decreased by the spinal anesthesia in some and increased in others.

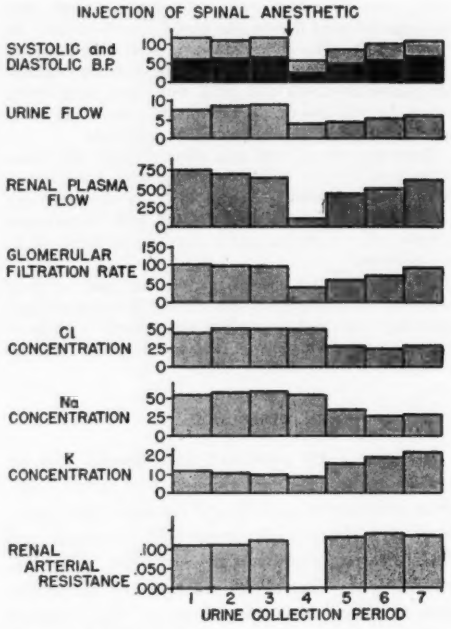

FIG. 2. MEAN VALUES FOR ALL FIVE CASES OF SYSTOLIC AND DIASTOLIC BLOOD PRESSURES, URINE FLOW, RENAL PLASMA FLOW, GLOMERULAR FILTRATION RATE, Cl, Na AND K CONCENTRATIONS AND RENAL ARTERIAL RESISTANCE

The blood pressure readings are in terms of mm. Hg. UF, RPF and GFR are calculated per 1.73 M^2/min. Concentrations of Cl, Na and K are in mEq/L.

Figure 2 presents the time relationship and the mean values of blood pressure, urine flow, electrolyte concentrations and clearances of mannitol and PAH in the post-loading periods before and after the spinal blockade. The renal arterial resistance is also indicated after the spinal blockade. Figure 3 presents the findings in subject J. S. who was selected as typical of the series.

[5] Because of the small quantities of procaine used in normal pregnant patients, it was considered unlikely that falsely high plasma levels of PAH due to entrance of procaine in the blood would result and thus interfere with the clearance determinations.

[6] The mean renal arterial resistance was calculated according to the formula of Lauson, Bradley and Cournand (12). The formula of Scheinberg and Stead (13) was used for calculation of mean arterial blood pressure. The figure given is actually based on renal plasma flow instead of renal blood flow since hematocrit determinations were not made.

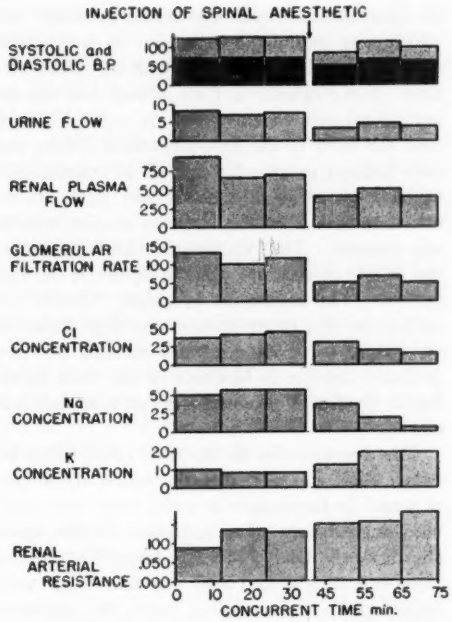

FIG. 3. CASE J. S. SYSTOLIC AND DIASTOLIC BLOOD PRESSURES, URINE FLOW, RENAL PLASMA FLOW, GLOMERULAR FILTRATION RATE, Cl, Na AND K CONCENTRATIONS, AND RENAL ARTERIAL RESISTANCE

The units of measurement are the same as for Fig. 2.

DISCUSSION

High spinal blockade in the normal pregnant woman affords a unique opportunity of studying the response of renal function to a marked drop in blood pressure since this marked drop is not obtained in the normal non-pregnant individual. Smith and his associates (14) studied the effect of spinal blockade in the normal non-pregnant subject and found no consistent pattern in the changes in renal hemodynamics. Hoobler and coworkers (15) made similar observations using tetraethylammonium chloride (TEAC). In both instances the changes in blood pressure were transient or inconstant. Mokotoff and Ross (16) found no alteration in the renal circulation of patients with congestive heart failure subjected to high spinal anesthesia and in whom the blood pressure was maintained at high levels by the use of ephedrine.

Renal function has been studied in patients with essential hypertension following lumbodorsal sympathectomy, spinal anesthesia and renal denervation (17–23). The results have varied according to the nature of the procedure and experimental conditions.

In patients with toxemia of pregnancy studied under high spinal anesthesia Turner and Houck (24) found a drop in glomerular filtration rate and renal plasma flow in each instance where there was a significant drop in blood pressure. In most cases the renal resistance was increased. They suggested that constriction of the renal arterioles was produced by some humoral agent following spinal anesthesia. Observations on hemorrhagic shock in man and animal (12, 25–27), as well as in the post-syncopal state (28), have shown a reduction in renal blood flow and glomerular filtration rate and an increase in renal arterial resistance in most cases where there was a significant drop in the systemic blood pressure accompanied by a drop in the cardiac output.

The analysis of the data presented in this paper leaves little doubt that the reduction in renal plasma flow and glomerular filtration rate produced by high spinal anesthesia in the pregnant woman is caused primarily by the marked drop in blood pressure. Nevertheless, calculation of the renal arterial resistance in the five cases studied showed that the spinal blockade did not produce vasodilatation in the renal blood vessels. Instead there was a tendency toward vasoconstriction as is indicated by a rise in the renal arterial resistance. Since the spinal blockade is effective in blocking autonomic vasoconstrictor fibres (1, 29, 30) it must be inferred that this increase in renal vasoconstriction is caused by a compensatory mechanism which is probably humoral in nature. This hypothesis has been suggested previously (1), following the observation that the blood pressure frequently returns to normal levels despite the maintenance of a high spinal anesthesia. Observations on the action of epinephrine under similar conditions of osmotic diuresis (31, 32) have shown that infusion of this agent produces effects similar to those observed here; *i.e.*, a reduction in urine flow, GFR, RPF, and in Cl and Na concentrations. It seems possible, therefore, that epinephrine or an epinephrine-like substance may be lib-

erated into the blood stream in response to the shock-like state observed during spinal anesthesia. Theobald, and Theobald and Verney (10, 11) in their experiments on the inhibition of water diuresis by emotional stress concluded that pitressin was responsible for the effects which they observed. In our cases this does not seem likely. The procedures reported here were carried out under conditions of osmotic diuresis in dehydration during which the water-conserving powers of the kidney were being subjected to severe strain and it must be assumed that maximal pitressin-like activity is present prior to induction of the spinal anesthetic. The possibility that these effects are due to liberation of larger quantities of pitressin which then induce active renal vasoconstriction is rendered even less likely since, rather than chloruresis which is an effect of pitressin injection, there was a reduction in chloride excretion.

It has been suggested (1, 2) that the fall in blood pressure which follows autonomic blockade with high spinal anesthesia is due either to a pooling of blood in the lower extremities with a concomitant decrease in cardiac output or to a generalized blockade of compensatory vasoconstrictor mechanisms. The data presented in this paper show that active vasoconstriction was proceeding in the kidney during maintenance of the anesthesia and, therefore, would tend to negate the hypothesis that there was paralysis of homeostatic vasoconstrictor mechanisms. The gradual return of blood pressure to normal values despite maintenance of anesthesia is further evidence of increase in the peripheral resistance despite continuation of the autonomic blockade. We are inclined to the belief, therefore, that the drop in blood pressure is due to diminution of venous return owing to pooling of blood in the lower extremities with subsequent reduction in cardiac output and blood pressure.

Concerning the effects of the autonomic blockade *per se* on renal function little can be said from the present set of experiments. In animals, after unilateral splanchnic nerve section (31, 32), osmotic diuresis with mannitol in dehydration is followed by increased sympathetic discharge to the opposite kidney which we believe is part of the general vasoconstrictor response to maintain blood pressure. This results in a reduction of Na and Cl concentrations on the non-denervated side which also exhibits a reduction in urine flow, GFR and RPF as compared with the denervated side. If epinephrine is then infused into the experimental animal both sides are equalized at or near the level of the non-denervated kidney and both kidneys excrete Na and Cl in reduced concentrations; urine flow, GFR and RPF are reduced on both sides, the filtration fraction remaining constant. Thus epinephrine discharge masks the effects of section of the sympathetic nervous system. The alterations in kidney function described in this paper closely resemble those observed in these experimental animals and are probably not due to blockade of the renal nerves but to discharge of epinephrine or a related substance.

The discrepancies in the time relationship between GFR and electrolyte excretion are worthy of note. In those cases in which they were measured immediately after induction of the spinal anesthetic the GFR and RPF dropped in the first urine collection period after injection of the anesthetic agent. On the other hand, the concentrations of Na and Cl did not drop until several minutes had elapsed after the injection of the spinal anesthetic. The rise in concentration of K, likewise, did not occur until an interval of time elapsed following injection of the spinal anesthetic. Furthermore, despite the return of GFR to control levels by the end of the procedure the concentrations of Na and Cl tended to remain at the reduced level. Thus an overall lack of correlation between GFR and electrolyte excretion is evident.

SUMMARY AND CONCLUSIONS

1. Renal hemodynamics and the excretion of electrolytes were studied during osmotic diuresis in five hydropenic normotensive pregnant subjects before and during high spinal anesthesia.

2. A marked reduction in urine flow, renal plasma flow and glomerular filtration rate was observed during the blood pressure fall following the spinal blockade. The filtration fraction did not change.

3. The excretion of Na and Cl was reduced following the blockade. This reduction did not bear any time relationship to the reduction in

glomerular filtration rate. The effect on K excretion was variable.

4. The changes in the renal circulation following the spinal blockade were probably produced by two factors:

a) decrease in the renal blood flow due to the blood pressure fall.

b) active compensatory renal vasoconstriction mediated by a humoral agent which tended to counteract the blood pressure fall.

5. It is suggested that epinephrine or an epinephrine-like substance might be the agent responsible for the renal vasoconstriction.

6. The present study supports the hypothesis that the blood pressure fall during spinal anesthesia in the pregnant woman is caused by excessive pooling of blood in the lower extremities and decrease in the cardiac output.

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EVALUATION OF NEUROGENIC CONTROL OF BLOOD PRESSURE IN HYPERTENSION WITH TETRAETHYLAMMONIUM CHLORIDE AND SPINAL ANESTHESIA [1]

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The contribution of sympathetic constrictor impulses to arteriolar tone is now recognized as playing an important though sometimes variable role in the maintenance of increased peripheral resistance in some patients with hypertension. However, lack of a clear understanding of the exact nature of autonomic influences and of their importance in relation to other pressor factors has complicated the development and evaluation of therapeutic measures for hypertension which have as their aim the modification of the "neurogenic component." [3] Results obtained after surgical sympathectomy have seemed encouraging in certain patients, discouraging in others. It has become apparent that operative results are inconsistent and that the most striking inconsistency is the effect on the blood pressure. Difficult, too, is the choice of patients who may be expected to benefit from this type of treatment; no satisfactory method of selection has yet been suggested.

This study was undertaken in an effort to evaluate the nature of autonomic influences on blood pressure level as indicated by observations and comparisons of the responses to autonomic blockade with tetraethylammonium chloride [4] (TEAC) and spinal anesthesia to high thoracic levels.

MATERIAL AND METHODS

Twenty-four patients were included in the study. Eleven patients had malignant and 13 had benign hypertension. To determine the blood pressure effect of pharmacologic blockade of autonomic impulse transmission, TEAC in 3–5 cc. doses (300–500 mg.) was administered intravenously to all patients on from two to 12 occasions. All studies were conducted with the patients supine, and the injections were made rapidly, requiring no more than five seconds for administration. Observations of pupillary dilatation and abolition of sweating were accepted as clinical confirmation that autonomic blockade had been induced. In addition, in those patients who showed slight or moderate blood pressure depression following the drug, abolition of cold pressor reactivity was demonstrated to confirm autonomic block. Blood pressures were obtained by auscultation. The *control blood pressure* represents the mean of five or more measurements taken at one-minute intervals before TEAC administration and following stabilization of the pressure in the recumbent position. The lowest point to which the blood pressure descended in the first five minutes following injection has been termed the *TEAC floor,* and for the purposes of this study this has been accepted as indicating that portion of arteriolar tone which persists following the removal of active autonomic influence. Although multiple tests with TEAC were done on all patients, Table I includes only the results of the first test. The first experience with TEAC was selected since comparison was to be made with a single first experience with spinal anesthesia.

On a subsequent day the effect on the blood pressure of spinal anesthesia to high thoracic levels was determined in each of these patients. With the subject on a tilt table, anesthesia was induced by the intrathecal injection of 100–125 mg. of procaine hydrochloride dissolved in 2–2½ cc. of his own spinal fluid. Control blood pressures were obtained prior to anesthesia by the method described above. Immediately following the intrathecal injection, the patient was tilted 7–10 degrees head down, until the level of skin anesthesia to pin prick had risen to high thoracic levels. The patient was then returned to the horizontal position for the remainder of the study. In the majority of patients it was possible to confirm the anesthesia level to pin prick by the observation of well demarcated levels of sudomotor paralysis. Blood pressure readings were taken at minute intervals throughout the period of high anesthesia and were followed less frequently only after the level had receded below the thoracic segments. The mean of five consecutive blood pressure determinations during the period of the highest anesthesia level was taken as the *spinal blood pressure* floor. To-

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[3] As used here *neurogenic* has reference exclusively to mechanisms involving the functional integrity of the sympathetic nervous system. It is no longer tenable to consider *psychogenic* and *neurogenic* as synonymous terms since the utilization of humoral (non-neurogenic) pathways for emotional responses is now well-established.

[4] Etamon chloride supplied by Parke, Davis and Company, through the courtesy of Dr. E. C. Vonder Heide.

TABLE I

Patient	Diagnosis	First TEAC		Spinal anesthesia			Spinal and TEAC		
		Control B.P.	TEAC B.P. floor	Control B.P.	Spinal B.P. floor	Anes. level	Anes. level	Control B.P.	Spinal-TEAC B.P. floor
I. O.	M.H.	252/174	180/120	258/162	167/106	T_{5-6}	T_8	182/108	156/100
H. B.	M.H.	207/126	134/86	240/146	172/99	T_{4-5}	T_{7-8}	186/100	140/90
J. W.	B.H.	230/150	170/130	209/146	132/96	T_3	T_9	160/110	150/110
E. E.	B.H.	225/140	138/96	236/153	173/112	T_4	T_{6-7}	170/114	116/84
F. I.	M.H.	218/148	120/90	240/155	184/125	T_4	T_{7-8}	205/135	170/115
S. B.	M.H.	228/140	210/126	262/160	219/135	T_{5-6}	T_{6-7}	246/144	198/128
L. S.	B.H.	181/142	160/130	198/155	160/130	T_{4-5}	T_8	160/130	150/110
F. N.	M.H.	209/138	105/80	260/160	146/98	T_{4-5}	T_8	200/120	75/65
M. Ma.	B.H.	224/154	140/100	239/153	190/128	T_3	T_8	190/128	154/118
E. O.	B.H.	225/128	176/110	253/137	143/95	T_{4-5}	T_{7-8}	155/105	150/105
D. H.	M.H.	217/151	170/110	230/153	140/91	T_{2-3}	T_{3-4}	140/91	135/90
M. D.	B.H.	195/145	105/90	240/158	200/138	T_6	T_{6-7}	190/140	145/125
O. H.	B.H.	218/145	185/130	210/151	188/130	T_{3-4}	T_{6-7}	205/135	150/120
N. N.	M.H.	230/130	162/100	222/139	194/116	T_6	T_{6-7}	206/120	136/90
P. T.	M.H.	199/144	142/104	256/163	198/132	T_{5-6}	T_{7-8}	204/140	220/140
V. E.	B.H.	182/116	114/76	200/118	146/89	T_{4-5}	T_7	178/100	112/70
E. H.	B.H.	220/135	160/105	210/130	164/108	T_{4-5}	T_9	155/100	125/85
T. M.	M.H.	240/134	176/110	219/138	185/110	T_{3-4}	T_7	188/108	184/110
H. L.	M.H.	225/132	174/110	253/175	171/113	T_4	—	—	—
L. L.	B.H.	188/98	150/80	184/101	162/95	T_3	—	—	—
M. Mo.	B.H.	170/95	140/75	225/125	150/94	T_{3-4}	—	—	—
V. F.	M.H.	196/154	114/84	215/154	127/102	T_4	—	—	—
D. Z.	B.H.	150/103	135/95	170/122	141/107	T_{3-4}	—	—	—
E. B.	B.H.	199/120	134/86	204/123	180/119	T_{4-5}	—	—	—

ward the end of the experiment, usually after the upper anesthesia level had receded to the lower thoracic segments, and the blood pressure had begun to rise, the TEAC floor was again determined in 18 of the 24 cases.

RESULTS

The results are summarized in Table I. In all patients, the blood pressure was reduced significantly by both TEAC and spinal anesthesia whether administered separately or in combination. There was a clear parallelism between the degree of blood pressure fall to the two procedures, and the blood pressure floors achieved by autonomic blockade with TEAC were slightly but significantly lower than the floors obtained with spinal anesthesia to levels ranging from T_6 to T_3.

Despite individual differences in magnitude of the depressor response at similar levels of spinal anesthesia, it was noted in all cases that the greatest reduction in blood pressure occurred when the anesthesia level was highest. As anesthesia receded from the higher spinal segments the blood pressure ascended in parallel fashion. There was, however, much individual variation in the rate of blood pressure recovery to control levels and such levels were rarely achieved during the period of observation even though evidences of anesthesia had disappeared.

It was repeatedly noted that control blood pressure levels were consistently higher than usual just prior to induction of spinal anesthesia. This seemed to correlate with other evidence of anticipatory anxiety which was observed to diminish as the experiment proceeded and may explain the failure of the blood pressure to return to preanesthetic levels in many cases. There was a similar but less marked tendency for the control blood pressure to be higher than usual before the first test with TEAC, and subsequent TEAC testing revealed a general trend to slightly lower control blood pressures when the experience was repeated.

In only four of the 24 patients studied was a lower blood pressure level obtained with high spinal anesthesia than with the TEAC test performed previously. Comparison of the differences between the spinal anesthesia floor and the first TEAC floor shows that the TEAC floor is significantly lower for this group of patients (systolic, p less than 0.02; diastolic, p less than 0.01).[5]

[5] Because of space limitations only data relating to the first TEAC test are reported. However, analysis of the difference between the spinal floor and the closest temporally related TEAC floor, and the means of all TEAC floors showed likewise a high degree of statistical significance.

Spinal anesthesia lowered the blood pressure from a mean control level of 226/145 mm. Hg to 168/111 mm. Hg. Mean control blood pressure before TEAC was 210/131 mm. Hg, and the mean TEAC floor was 150/101 mm. Hg.

In 12 patients the upper level of anesthesia achieved was between T_6 and T_4. For this group the mean difference between spinal floor and first TEAC floor was 27.2/18.7 mm. Hg. In the remaining 12 patients anesthesia height was from T_4 to T_2 and the mean floor difference 10.9/7.8 mm. Hg. Thus, although specific patient to pa-

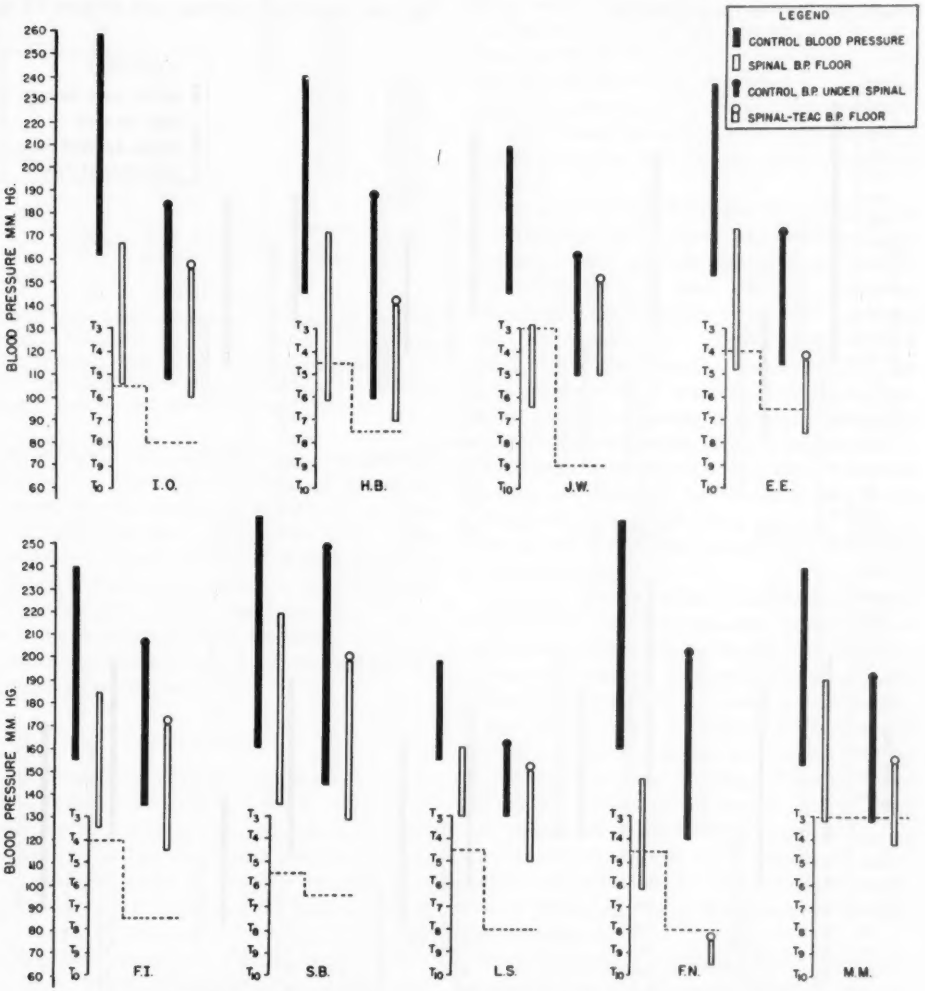

FIG. 1. COMPARISON OF SPINAL AND SPINAL-TEAC BLOOD PRESSURE FLOORS

The columns as indicated in the legend represent blood pressure levels which may be read from the scale at the extreme left. The dotted line extending from the spinal segment scale indicates the upper level of spinal anesthesia at the time of the blood pressure observations.

tient correlations of anesthesia level and blood pressure level are not feasible, there is a definite trend for the spinal anesthesia floor to approach the TEAC floor as the level of anesthesia is carried higher. These observations have served to focus attention on the upper thoracic segments as mediating a significant portion of the sympathetic constrictor tone in these patients.

In 18 patients the TEAC floor was again determined during the period of spinal anesthesia, usually after anesthesia had begun to recede from the higher thoracic segments. Individual results are shown in Figures 1 and 2. The mean TEAC floor under spinal (148/103 mm. Hg) was 25/10 mm. Hg lower than the spinal floor (173/113 mm. Hg) and was almost identical with the first TEAC

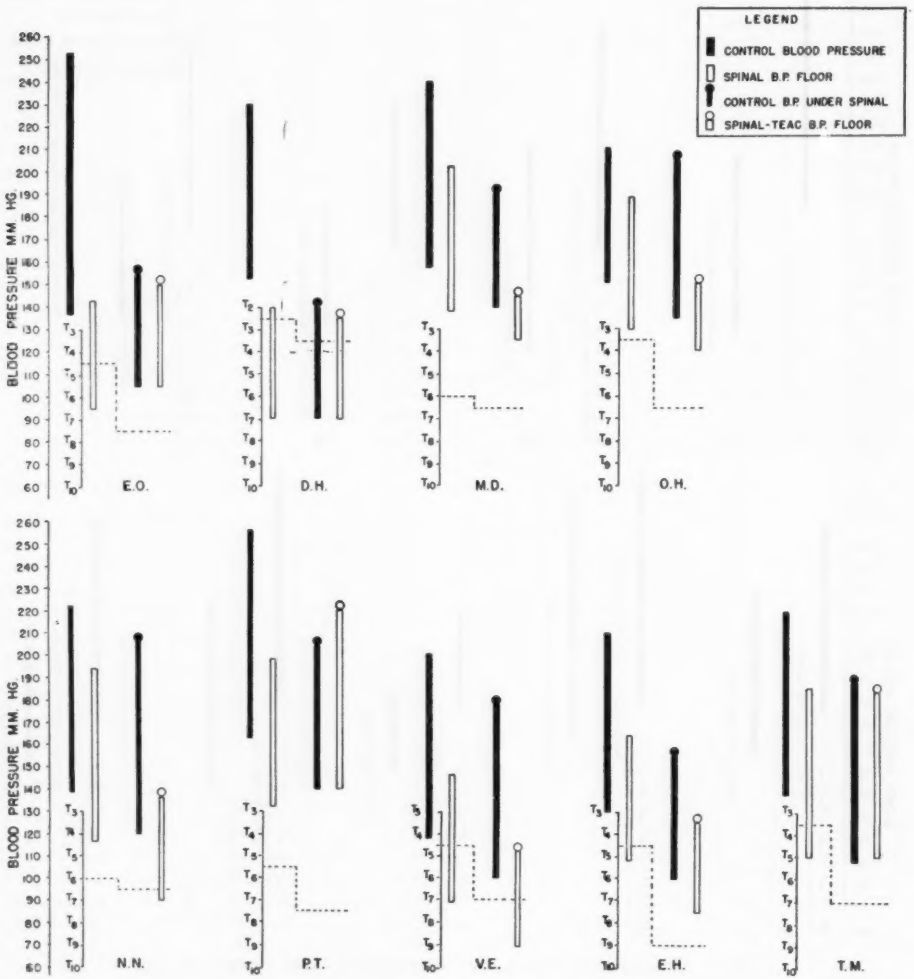

FIG. 2. COMPARISON OF SPINAL AND SPINAL-TEAC BLOOD PRESSURE FLOORS
For explanation see Figure 1.

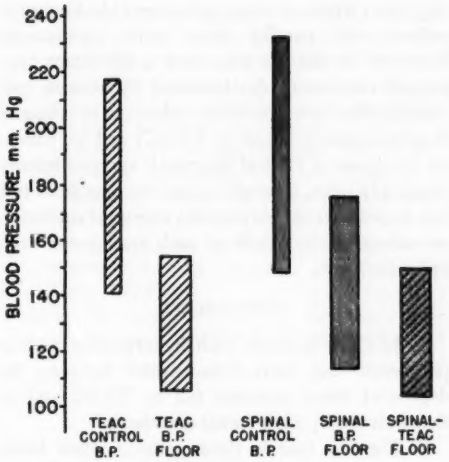

FIG. 3. COMPARISON OF MEANS

Mean blood pressure responses of 18 patients who, following an initial test with TEAC, received the same drug during receding high spinal anesthesia on a subsequent day. Note the similarity of the initial mean TEAC blood pressure floor to that obtained during anesthesia.

floor (153/105 mm. Hg) for these same patients (Figure 3). Statistical evaluation of the differences between the spinal floor and the TEAC floor under receding spinal anesthesia reveals a high degree of significance (systolic and diastolic, p less than 0.01) whereas comparison of the differences between the first TEAC floors and the TEAC floors under receding spinal anesthesia shows no statistical significance (systolic, p greater than 0.5; diastolic, p greater than 0.7).

DISCUSSION

The blockade of autonomic ganglia induced by TEAC and the pre-ganglionic block achieved by high spinal anesthesia exhibit certain hemodynamic similarities. It is generally accepted that the arteriolar dilatation which is observed with both procedures occurs as a result of the interruption of tonic vasomotor impulses and reflects a diminution in peripheral resistance. Cardiac output is not reduced by TEAC (1) and need not change after spinal anesthesia. Harrison (2) emphasizes that when cardiac output does fall during spinal anesthesia, the fall occurs secondarily, *i.e.*, follows rather than precedes any reduction in blood pressure. Studies by Milwidsky and de Vries on intramuscular pressures (3) and by Sarnoff and Arrowood with differential spinal block (4) have offered added support to the concept that sympathetic constrictor paralysis is the principal mechanism involved in the reduction of blood pressure during spinal anesthesia.

Questions as to the completeness of the ganglionic block by TEAC have been raised. Evidence presented here and elsewhere (5) indicates that for the purpose of blood pressure evaluation in acute intravenous experiments, the block is sufficiently complete although of rapidly transient nature.

Thus in this study of patients with hypertension an attempt has been made to compare blood pressure levels after relatively complete sympathetic block (TEAC) with those obtained during an anatomically less complete sympathetic paralysis (high spinal anesthesia). The results demonstrate clearly that in the majority of cases studied, the blood pressure falls to lower levels in response to TEAC block than during high spinal anesthesia regardless of whether the TEAC is given alone or during receding anesthesia. A further indication of more complete block by TEAC is seen in the tendency for the spinal blood pressure floor to approach the TEAC floor as the anesthesia level is carried higher.

Maximum blood pressure reduction at the highest anesthesia level and progressive blood pressure rise as the anesthesia level recedes are consistent with the observations of Russek, Southworth and Zohman during continuous caudal anesthesia (6). It thus appears that in these cases of hypertension there is a direct relationship between the level of the blood pressure and the extent of the arteriolar bed under active vasomotor control. All of these observations substantiate a 1932 report by Ferguson and North (7) that the amount of blood pressure fall which occurs with spinal anesthesia bears a direct relationship to the number of white rami anesthetized.

Since the degree of additional fall in blood pressure induced by TEAC varies widely in different patients with spinal anesthesia of comparable extent in the current study, it appears that the remaining portion of the arteriolar bed (unanes-

thetized portion) which is capable of exerting pressor activity varies from patient to patient. This observation may help to explain the lack of uniform blood pressure responses when sympathetic resections of standardized extent are performed on large groups of patients. It is of interest that in a parallel study of the cold pressor test (8), it was found that neurogenic control of cold pressor reactivity follows the same pattern as seen here for the neurogenic vasomotor mechanism.

Taylor and associates (9) were unable to derive other than negative value from pre-sympathectomy spinal and caudal anesthesia studies in hypertensive patients. Soloff and coworkers (10), using tetraethylammonium bromide and spinal anesthesia likewise found that they could not consistently predict post-operative blood pressure levels. The TEAC floor has been interpreted here to reflect that component of arteriolar tone which is relatively devoid of sympathetic control. It has previously been reported that in some patients this floor may vary considerably from day to day (11), and hence that such variation may represent fluctuation of interacting neurogenic and humoral (non-neurogenic) mechanisms. Some of the patients in this study who had repeated TEAC tests likewise showed this variability. Whether similar and parallel fluctuations in the response to spinal anesthesia occur in these same patients was not determined here. Current evidence for day to day variability of the neurogenic component in many hypertensive patients may help account for the apparent discrepancies in pre-operative predictions and post-operative observations. Repeated pre-operative study of the blood pressure effects of sympathetic block in a given patient may offer a clue to the degree of variability of the neurogenic component in the individual case. Inconsistent post-operative blood pressure results thereby become more meaningful when pre-operative variability to autonomic block has been established. In our experience, repeated testing with TEAC may be required to assess the degree of consistency or variability of response. It should be remembered that the results of this study represent the immediate effects of acute disruption of the homeostatic mechanisms involved in blood pressure maintenance. It need not necessarily follow that the long term effects of more permanent blocking procedures will parallel these acute phenomena. However, in patients who show a significant neurogenic component (as indicated by sizeable and reproducible blood pressure reduction in response to spinal anesthesia and/or TEAC) and for whom, on the basis of clinical appraisal, sympathectomy seems advisable, it would appear reasonable to test this hypothesis by varying the extent of operation according to the result of such testing for each individual case.

CONCLUSIONS

1. In these patients with hypertension a clear parallelism has been demonstrated between the degree of blood pressure fall to TEAC and to that induced by high spinal anesthesia.

2. The fact that in these patients lower blood pressure levels were obtained with TEAC than with high spinal anesthesia, plus the ability of TEAC to reduce the blood pressure further when administered during high spinal anesthesia, provide additional evidence that the pharmacologic autonomic blockade which this drug induces is relatively more complete than that which occurs with the block of extensive but anatomically incomplete spinal anesthesia.

3. In these patients the level of the blood pressure tended to vary indirectly with the level of spinal anesthesia.

ACKNOWLEDGMENTS

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STUDIES OF CORONARY DISEASE IN THE EXPERIMENTAL ANIMAL. II. POLAROGRAPHIC DETERMINATIONS OF LOCAL OXYGEN AVAILABILITY IN THE DOG'S LEFT VENTRICLE DURING CORONARY OCCLUSION AND PURE OXYGEN BREATHING[1]

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In experiments previously reported (1) it was found that platinum electrodes for polarographic measurement of oxygen availability have given fairly steady control readings in the left ventricular muscle of the dog. When the animals breathed pure oxygen, electrode readings rose 50–200%. When a coronary branch was occluded they declined considerably at the borders of the ischemic area, approached zero at its center, and returned to the base line shortly after release of the ligature. If the artery was occluded with the dog breathing room air, pure oxygen breathing did not change values at the center of the ischemic area. However, it did cause a rise in the readings at the "borders" *before* the occlusion was released. These conclusions were based on studies of 12 anesthetized dogs using two or three electrodes simultaneously in each experiment.

We have since developed a more stable dog preparation, using larger numbers of electrodes and obtaining more frequent readings which give a more complete description of the changes in local oxygen availability during short periods of coronary occlusion. Our particular concern has been to learn the size of the "border" areas that may be favorably affected by oxygen inhalation as well as the magnitude and regularity of the oxygen effect. This paper will describe the method we now use, and present a statistical analysis of the results of the first seven experiments in which we have used it. These studies would seem to have a bearing on the use of oxygen inhalation for the treatment of acute myocardial infarction in man.

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METHOD

Apparatus. In our earliest experiments we used the polarographic apparatus described by Montgomery and Horwitz (2) for use in the skin. Since then certain modifications have been made. We now use continuous electrolysis with six to 10 electrodes in the circuit at all times, their individual current variations being recorded when desired on a D'Arsonval galvanometer with a sensitivity of 5×10^{-10} amps./mm. The circuit modification is shown in Figure 1 and described in its legend. Open tip platinum electrode construction and the principles of polarography as applied to animal tissues have been described by Davies and Brink (3) and Montgomery and Horwitz (4). For the indifferent electrode we have found it necessary to immerse the dog's entire hind foot in a glass dish of saturated NaCl solution from which contact is made to the salt bridge of a calomel half cell. For electrode connections to the switch box No. 30 plain enameled wire was further insulated by placing it inside vinyl tubing.

Anesthesia and gas administration. Healthy dogs weighing 15–22 Kgms. were given morphine sulfate intramuscularly (3 mg./Kgm.) followed in 45 minutes by slow intravenous injection of 0.25 cc./Kgm. of a mixture containing equal parts of Nembutal (60 mg./cc.) and Dial-Urethane (Ciba). This combination had the advantage of producing a relatively slow heart rate and no more than a moderate blood pressure fall. Pure oxygen or mixtures of oxygen and nitrogen were administered through a tracheal tube made to fit the trachea snugly by a balloon and connected to a breathing bag through a soda-lime cannister. The exhaust valve of the bag was left partly open for gas mixtures which were delivered with flows of 6–8 liters/minute.

Manual insufflation was carried on by intermittent pressure on the bag every 10–15 seconds from the time the thoracic cavity was opened till the end of the experiment.

Surgery. A sternum splitting incision was made, using aseptic technique only in the occasional animal for

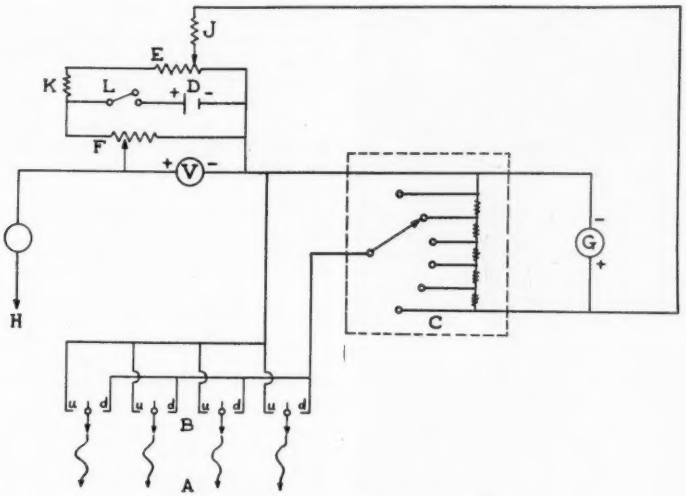

FIG. 1. WIRING DIAGRAM OF CIRCUIT

A. Electrodes (cathodes)
B. Micro-switches
C. Ayrton shunt (Rubicon No. 1243), resistance 65,000 ohms
D. Dry cell (1.5 volts)
E. Variable resistance, 10,000 ohms
F. Variable resistance, 500 ohms
G. Galvanometer (Rubicon No. 3418)
H. Connection to calomel half-cell (anode)
J. Fixed resistance (2,000,000 ohms)
K. Fixed resistance (40,000 ohms)
L. Main switch
V. Voltmeter (1000 ohms per volt)
u. "Up" position (ordinary) of micro-switch
d. "Down" position.

The circuit described by Montgomery and Horwitz (4) has been modified by substituting micro-switches for the selector switch so that any number of electrodes in parallel (up to 10) may remain in the electrolysis circuit, the individual currents for each being read on the galvanometer by depressing (d) the micro-switch for the particular electrode. See text for connections of cathodes and anode to the animal.

which survival was planned. The pericardium was opened and stitched to the incision edges to form a cradle for the heart. One or two branches of the anterior descending coronary artery were dissected free from their accompanying veins and braided silk ligatures placed ready for traction. Warm saline was applied frequently to the heart.

Electrode placement. The tips of six to 10 electrodes were inserted through the epicardium 2–3 mm. into the myocardium by simple pressure, each electrode resting lightly on the flange where its tip passed into the shaft, supported only by the wire which had been inserted into the mercury-filled glass shaft and covered by vinyl tubing. The wire arched from the electrode's butt to a rubber-shod Allis forceps at the incision's border (Figure 2), from which point of fixation it ran to the switch box. The simple arch of wire and vinyl tubing plus the weight of the electrode shaft proved superior to any more elaborate methods of support and enabled the electrodes to ride smoothly with the ventricular motion. Steady currents of the order of 10^{-7} amps. were recorded shortly after electrolysis at 0.6 volt was begun. If any electrode gave very low or irregular readings, the angle of insertion or the site was changed slightly, otherwise the electrodes were not touched during an experiment.

It proved best to start the animal breathing room air just after electrode insertion and to test the electrode sensitivity by a shift to pure oxygen, which caused all

FIG. 2. SEVEN ELECTRODES INSERTED IN THE ANTERIOR SURFACE OF A DOG'S LEFT VENTRICLE DURING AN EXPERIMENT

See text for a description of their connections and support. The head of the animal is beyond the upper margin of the picture. The sternum has been split and the heart is supported in a cradle of pericardium, sewn to the incision's edges.

values to rise barring mechanical or electrical faults. A drawing was then made of the topography of the exposed left ventricle including the major ramifications of all visible coronary branches and the sites of electrodes. Later, after observation of the effects of coronary occlusion, the distribution of cyanosis and systolic bulging were added to the drawing and the electrodes were classified on the basis of their apparent relation to the occluded coronary ramus and ischemic area as "center," "border" and "outside." Figure 3 shows the drawings for all seven experiments.

Procedure

(*1*) *Control readings:* Electrodes were read in rotation, six to nine seconds being required for galvanometer stabilization. The time at which each series of readings began was recorded. Before any occlusion or other procedure a base line was obtained on all electrodes consisting of three readings which did not differ in the case of any electrode by more than 15%.

(*2*) *Occlusion without oxygen:* With strong traction occluding the coronary ramus, electrode readings were obtained during a three minute period and the two to five minutes required for return to a steady state after release.

(*3*) *Occlusion, with oxygen before release:* With the animal inhaling room air the coronary branch was again occluded and after at least two series of readings during the occlusion, 100% oxygen was substituted for air. The bag was flushed twice to facilitate the change. Two or three more series of readings were recorded and the occlusion was then released. The changes during the recovery period were studied for several minutes. Room air was then substituted for oxygen and additional readings were recorded.

RESULTS

The characteristic changes at 58 sites of insertion of the electrodes are summarized in Figure 4 and Table I. The division of electrodes into "center," "border" and "outside" groups was done as described above *without reference to the electrode data.* It can be seen that fairly good correlation exists between the distribution of the electrodes with respect to the visibly ischemic area and their types of behavior. The "central" electrode values drop sharply after coronary occlusion, their values remaining low until release regardless of oxygen breathing. Remote electrode readings show no statistically significant changes during or after occlusion except for their constant response to oxygen breathing. "Border" electrodes give figures similar to "central" electrodes except for a significant rise during oxygen breathing before termination of occlusion. During recovery from occlusion high values are recorded at all areas previously ischemic but there is no significant further rise at the "outside" electrodes. The post-occlusional increases in oxygen availability are greater at the "centers" of previously ischemic areas and after oxygen administration. With a combination of those circumstances the highest values were attained.

Records typical of the figures obtained from a "center," "border" and "outside" electrode during three occlusions without oxygen and two occlusions with oxygen before release are shown in Figure 5. The absolute values recorded by the galvanometer have been converted into percentages of a repre-

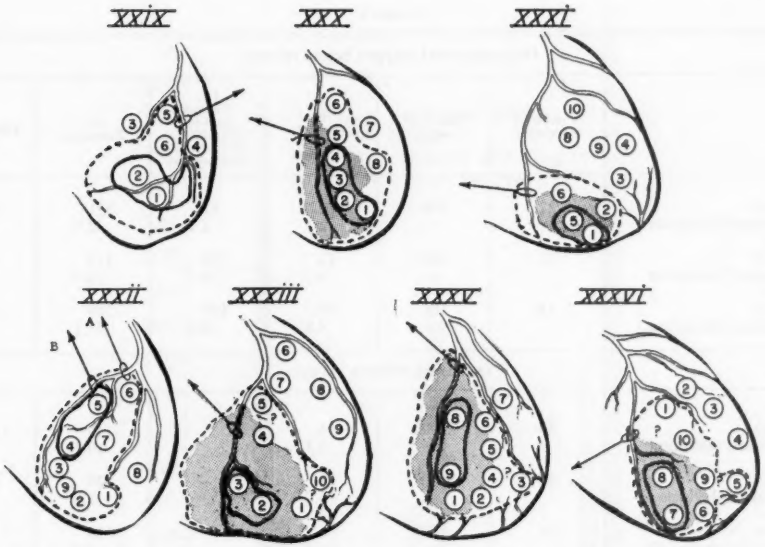

FIG. 3. THE POSITION OF ELECTRODES IN RELATION TO THE CORONARY VESSELS, LOCATION OF LIGATURE AND VISIBLE EXTENT OF THE ISCHEMIC AREA IN SEVEN EXPERIMENTS

In XXIX and XXXII no cyanosis or definite borders of the ischemic area could be seen although systolic bulging occurred in the distribution of the occluded coronary branches. Consequently there is a shaded region in only five of the drawings. The question marks in XXXIII, XXXV and XXXVI indicate areas of slight discoloration thought to be within the ischemic zone. The solid lines enclose the areas in which electrode positions were considered "central" on anatomic grounds for the purposes of the statistical analysis. The broken lines enclose the "border" electrode positions.

sentative initial base line reading for each electrode. The patterns of change in oxygen availability at each electrode with repeated occlusions of the same coronary ramus tended to be fairly constant. Longer occlusions caused larger changes to be recorded at "border" areas because of their slower rate of fall. "Center" electrodes tended to fall close to zero within three minutes of the beginning of occlusion. They were generally unaffected by oxygen breathing prior to the release of occlusion, whereas outside electrodes showed rapid rises and many "border" areas showed slighter but distinct rises. A minority of electrodes outside the ischemic area showed slight increases of oxygen availability during occlusion as shown by electrode No. 1 in Figure 5. Since muscle color and contraction seemed normal in such areas, the changes were thought to reflect increased circulation.

When no coronary occlusion was produced, rises in electrode currents with pure oxygen breathing were almost universal though the amount of rise varied widely. Failure of such a rise to occur was almost always attributable to some defect in an electrode or its connections. Slighter rises occurred with 50% oxygen breathing and falls below the base line occurred with 10% oxygen breathing, characteristics which will be reported in a later paper.

The effect on electrode values of parenteral epinephrine administration was comparable in direction and magnitude to that of pure oxygen inhalation. It appeared to be independent of the oxygen effect. These phenomena will be reported in detail later when the results of longer periods of observation can be evaluated. Ventricular fibrillation, which occasionally occurred at the end of an experiment, caused all electrode readings to drop rapidly to zero and remain there.

TABLE I

	Number of electrodes	Base line value	(A) Lowest reading during occlusion	(B) Highest reading after 100% oxygen and before release	(C) Recovery	(D) Final steady state
Occlusion, with oxygen before release						
Center						
Mean	22	100	12	17	321	192
Standard deviation		—	2.4	4.3	32.9	8.3
Border						
Mean	41	100	73	125	219	114
Standard deviation		—	8.1	14.7	24.9	7.4
Outside						
Mean	18	100	97	185	298	134
Standard deviation		—	8.8	26.9	72.1	10.4
Occlusion without oxygen						
Center						
Mean	30	100	14		149	106
Standard deviation		—	3.1		10.1	3.2
Border						
Mean	48	100	72		129	109
Standard deviation		—	6.2		5.8	5.2
Outside						
Mean	31	100	88		113	97
Standard deviation		—	11.1		8.3	4.2

Readings selected from central, border and outside electrodes, the last base line reading being taken as 100%: (A) The reading showing the largest change from the base line during occlusion, (B) the highest value during oxygen administration before release, (C) the highest value during the first three minutes of recovery from occlusion, and (D) the final reading after the animal had again been stabilized on room air. Standard deviations are given for the mean values in each instance.

TABLE II

Physiological classification of electrode areas

	Total number of occlusions with or without oxygen	Number of occlusions with oxygen before release	Number of electrodes	Mean oxygen effects before release			
				Rise over 25%*	Rise 5–25%*	Rise less than 5%*	Falls
Group I "Center" Mean fall to below one-fourth of base line value	50	22	14	1	2	8	3
Group II "Border" Significant mean fall but less than Group I	91	44	28	14	5	4	5
Group III "Outside" Mean fall† less than 15%*	56	25	16	11	3	0	2‡

* Of the pre-occlusion base line value.
† Rises occurred at seven electrodes.
‡ These falls followed large rises during occlusion.

The left half of this table shows a classification of all electrode areas based on the mean fall during occlusion and before oxygen (if given). The three groups, which are "center," "border" and "outside" areas *physiologically*, are not incompatible with the anatomic areas seen in Figure 3.

The approximate magnitude (in terms of the pre-occlusion base line value taken as 100%) and the frequency of pre-release rises in response to inhalation of pure oxygen are given for the three physiological groups in the right-hand half of the table.

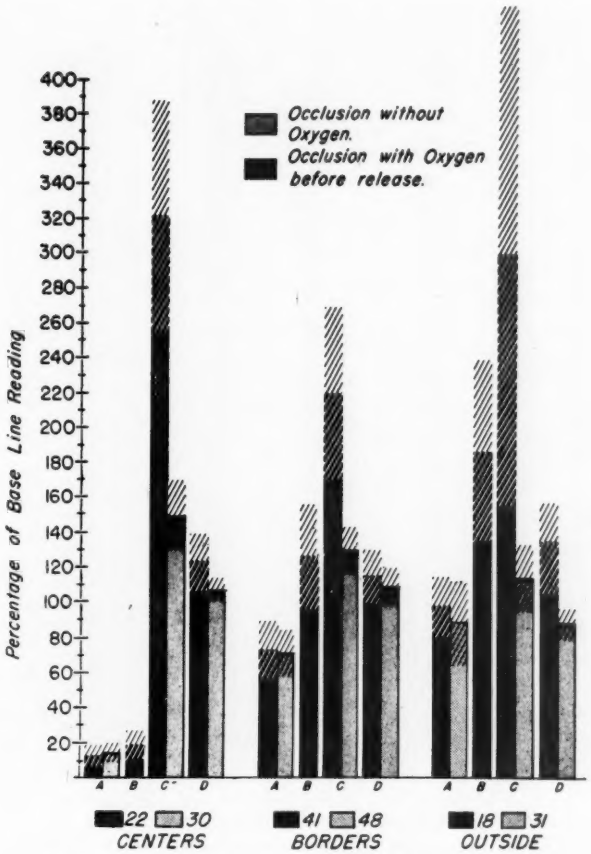

FIG. 4. BAR GRAPH OF THE MEAN VALUES GIVEN IN TABLE I

The two types of occlusion are distinguished by black and gray, while the cross-hatchings represent *twice* the standard deviation of values above and below the mean for each group of determinations, the number of these in each case being given below the graph. The initial base line readings are not given since they were taken as 100%. The paired or single bars for each group of electrodes correspond to columns two through five of Table I: that is, (A) maximum fall with occlusion, (B) change with oxygen before release, (C) recovery, (D) return to steady state. Note especially the means of border electrodes at (A) and (B) and the significant difference between them.

DISCUSSION

Open tip platinum electrodes provide relative measurements of oxygen *tension* in homogeneous solutions (3). In the heart muscle, because a constant relationship between tension and diffusion of oxygen cannot be assumed, it is probably preferable to report the electrode measurements in terms of oxygen "availability." We have departed from the method used for skin by Montgomery and Horwitz (4) in which brief closures of the circuit presumably cause only short gradients of oxygen tension out from the electrodes with less

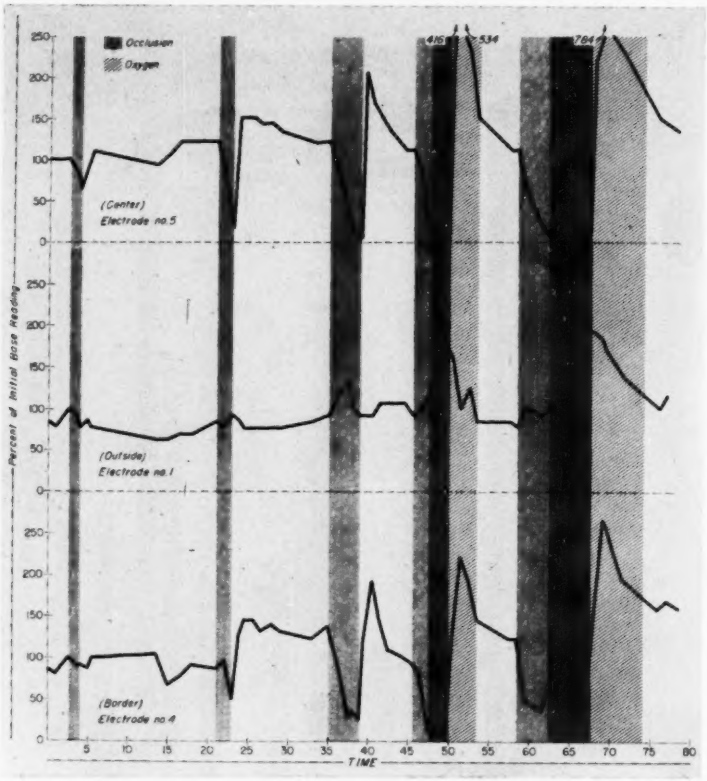

FIG. 5. GRAPH OF 60 VALUES READ ON THE GALVANOMETER FROM EACH OF THREE ELECTRODES THROUGHOUT EXPERIMENT XXXII.

Time is given in minutes from an arbitrary zero, just after which the base line value taken as 100% was selected. Occlusion is denoted by gray coloration, pure oxygen inhalation by cross-hatching, and oxygen *during* occlusion by superimposition of these. The first occlusion was at B (see Figure 3). Its effects were considered too localized and the more proximal site A was selected for the subsequent occlusions. A late but significant rise at electrode 4 (border) *before* release of the occlusion can be seen at 49 minutes. A longer and greater rise occurs from 62 to 67 minutes at the same electrode. No determinations were made between 71 and 75 minutes, so that the graph's downward slope during the last three minutes of pure oxygen breathing is misleading. Readings were at approximately one minute intervals throughout the experiment but are not, of course, simultaneous since nine electrodes had to be read in rotation each time.

chance of variation in diffusion gradients. In any case the current record in a myocardial electrode is the resultant of multiple factors including convection currents, the proximity of high capacity sources of oxygen such as red cells and alterations of the shape of the oxyhemoglobin dissociation curve by pH or temperature. Muscle contraction, with presumably intermittent oxygen utilization, must be a factor in the beating heart but the slow response of the d'Arsonval galvanometer does not permit study of such rapid fluctuations. Indeed, currents associated with cardiac excitation might prove difficult to distinguish from those due to oxygen reduction should a more rapidly responsive instrument be employed.

The interplay of all these influences makes the

platinum electrode of uncertain value at present for quantitative study of changes in the heart as a whole or the comparison of readings widely spread in time. Nevertheless it is a great advantage to have multiple and rapid or, if desired, continuous estimations of available oxygen when studying localized myocardial ischemia.

It is possible to make a "physiologic" division of the electrode areas according to their behavior during repeated occlusions rather than the "anatomic" division adopted for the initial correlation. Based on the mean of the greatest changes from the last control value during occlusions without oxygen and the pre-oxygen period of the other occlusions for each electrode, three myocardial zones can be differentiated. The characteristics of these physiologic areas are summarized in Table II. Figure 6 shows the electrodes assigned to "physiologic" groups, and the inferred extent of the "central" and "border" zones. Comparison with Figure 3 makes it clear that neither distribution is incompatible with the epicardial coronary distribution and the observed extent of the grossly ischemic areas.

Since the "border" areas cannot be sharply defined and their behavior cannot be predicted on purely anatomic grounds, the physiologic grouping seems to have advantages for describing the character of localized ischemic areas in the myocardium. It can be stated on the basis of our data so far that during short occlusions electrodes which fall significantly (more than 15%) but not below one-fourth of the base line value have shown rises on pure oxygen breathing during occlusion in 68% of instances. The majority of these rises have been greater than 25% of the base-line figure for the particular electrode. At areas showing falls to less than one-fourth of the base-

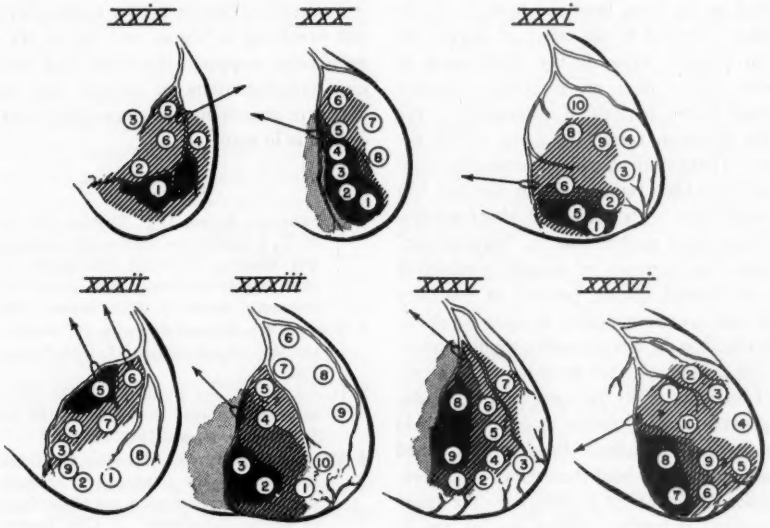

FIG. 6. THE APPROXIMATE EXTENT OF "PHYSIOLOGIC" CENTRAL (DARK) AND BORDER (HATCHED) ZONES, BASED ON THE MEAN OF MAXIMAL CHANGES IN ELECTRODE READINGS AT EACH POSITION DURING CORONARY OCCLUSION

The electrode position, coronary pattern and visible extent of ischemia (light shading) are identical with Figure 3, to which this figure should be compared. See text and Table II for further explanation. It is noteworthy that in experiments XXXI, XXXV and XXXVI electrode behavior indicates occlusion or stenosis of the coronary ramus at a higher point than the anatomic position of the ligature. This would not be impossible, because strong traction was used to produce occlusion. We are inclined to think that the electrode behavior reflects the actual consequences of experimental occlusion better than the "anatomic" classification of electrode areas shown in Figure 3.

line values, rises during oxygen breathing occurred in 22% of instances during occlusion with only a single instance of a rise larger than 25%. Areas in which electrode values rose with coronary occlusion or fell insignificantly were characterized by rises during oxygen breathing in 88% of instances, most of them greater than 25%.

It had not been established previous to our preliminary report that intramyocardial oxygen availability increases with pure oxygen breathing in a manner similar to that observed in human skin (2). How great an advantage to the normal myocardium this is remains conjectural at present, but the presumption must be that some portions of the borders of myocardial infarcts will remain viable as a result of pure oxygen inhalation. How large these areas may be would seem to depend on the severity of the ischemia, the length of the ischemic period, and the duration of increases in oxygen availability. The occlusions we have studied so far have been too brief to decide this question. Studies of the effect of oxygen inhalation on ischemic areas in the distribution of a narrowed rather than an occluded coronary vessel permit longer periods of observation. We believe this situation resembles many which occur in man. These studies, which are nearing completion and have been reported in an abstract (5) include correlation with epicardial electrocardiograms. They have shown that in "physiologic" border areas the increases of oxygen availability are well maintained during periods of coronary narrowing and are accompanied at least occasionally by diminution in electrocardiographic abnormality. The occasional rises recorded at "central" areas are transient. Fifty per cent oxygen inhalation has proved greatly inferior to pure oxygen in achieving favorable results. Preparations based on coronary narrowing lend themselves much better to studies of the effect of drugs on the heart during localized ischemia. These studies are in progress.

SUMMARY AND CONCLUSIONS

A polarographic technique for multiple, rapid, and relatively simultaneous estimations of local oxygen availability in the dog's left ventricular muscle has been described, together with some results of its application to the study of brief coronary occlusions. Electrode responses during coronary occlusion permit differentiation of three myocardial zones: (1) "Central" areas which show rapid decreases in available oxygen to less than a quarter of the base line values; (2) "Border" areas where falls are slower and less profound; (3) "Outside" areas showing no significant decrease in available oxygen. This physiological classification of myocardial areas has been consistent with the gross appearance of the heart when the borders of the ischemic areas are clearly discernible.

When pure oxygen inhalation is begun during coronary occlusion "outside" areas show the large and prompt rises of electrode readings characteristic of "normal" muscle, rises in "central" areas are rare and slight, while in "border" areas one-third of the initial fall is regained in two-thirds of instances. This statistically significant increase in available oxygen in border zones after pure oxygen breathing is begun, and before the occlusion terminates, supports the belief that inhalation of high concentrations of oxygen may reduce the extent of muscle necrosis resulting from coronary occlusion in man.

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PRIMARY AND SECONDARY LEUCOCYTE CHANGES FOLLOWING THE INTRAMUSCULAR INJECTION OF EPINEPHRINE HYDROCHLORIDE [1]

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An increase in the number of circulating leucocytes in human subjects following the parenteral administration of epinephrine has long been known to occur (1–4). Frey (2, 5) provided evidence to show that the leucocytes which appear in the circulating blood following administration of epinephrine are delivered, in part, from the spleen. Frey and Hagemann (6) and more recently Doan and Wright (7) have claimed that a significant alteration in the number of circulating formed elements of the blood from that which normally follows the injection of epinephrine reflects the activity of an abnormal spleen.

The test described by Doan and Wright (7) involves the subcutaneous injection of 0.5 to 1.0 mg. of epinephrine hydrochloride. The number of circulating erythrocytes, leucocytes, and thrombocytes, are determined at frequent intervals for a period of one hour, and the maximal change from pre-injection levels is noted. Despite the fact that well-delineated criteria for a positive test are lacking, Doan and Wright (7) and Kracke and Riser (8) use such response as evidence in favor of the diagnosis of the "hypersplenic syndrome."

More recently a different "epinephrine test," to be used in the evaluation of the functional integrity of the pituitary-adrenocortical system, has been reported (9–11). As described by Recant and associates (9) a small dose (0.3 mg.) of epinephrine hydrochloride is injected subcutaneously in the test subject. The eosinophils are enumerated by absolute count before the injection and four hours later. A decrease of 50% in the number of circulating eosinophils reflects an intact pituitary-adrenocortical system, and helps to rule out pituitary insufficiency syndromes. In the presence of a normal pituitary gland, the functional capacity of the adrenal cortex may be evaluated. Among the clinical syndromes to which the test may be applicable are hypopituitary states (9), Addison's disease (9, 10) and situations in which a low adrenal reserve may be a threat to the survival of the patient, as during surgery (11).

In the literature, therefore, two distinctly different "epinephrine tests" are described. The test, as utilized by Doan, is based on the immediate response ("primary phase") of the circulating formed elements to epinephrine, while the late or "secondary phase" following the injection of epinephrine is commonly used to refer to the activity of the pituitary-adrenocortical system. Although the general nature of this biphasic cellular response to epinephrine has been recorded (2, 12–15), detailed observations on the quantitative alterations of all components of the white cell series are not available. The purpose of this paper is to describe the alterations in the number of circulating leucocytes during both phases of the response to epinephrine in normal human subjects, and to show the relation of the primary phase (the immediate alterations) to the secondary phase (the delayed changes). A preliminary report of this work has appeared (16).

METHODS

Thirty-four subjects were studied. The patients were reclining, inactive, and fasting throughout the six hour period of the test. The contents of individual ampules, containing 1 ml. of a 1:1000 aqueous solution of epinephrine hydrochloride, were administered intramuscularly.

Venous blood samples were taken immediately before, and at five, 12, 17, 21 and 30 minutes, and one, two, four and six hours after the injection. A fresh venipuncture was made for each sampling and the blood samples were collected in bottles containing potassium and ammonium oxalate as anticoagulant (17). Cover-slip smears were made from the freshly-drawn specimens and stained with

[1] Supported in part by research grants from the National Heart Institute (USPHS) and the Ciba Pharmaceutical Company.

[2] Fellow in cardio-vascular research (USPHS).

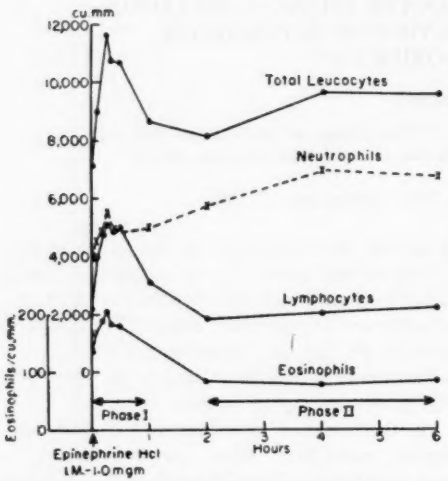

FIG. 1. THE AVERAGE CHANGE IN THE NUMBER OF CIRCULATING LEUCOCYTES IN 20 NORMAL HUMAN SUBJECTS FOLLOWING THE INTRAMUSCULAR INJECTION OF 1.0 ML. OF EPINEPHRINE HYDROCHLORIDE (1:1,000)

The curves are constructed from the average cell counts of all cases, the blood samples having been taken at the same intervals throughout, namely five, 12, 17, 21 and 30 minutes; two, four and six hours after injection.

Wright's stain. The total number of leucocytes was determined in the usual manner from duplicate dilutions. The absolute number of neutrophils and lymphocytes was determined by a count of 200–400 cells from the stained smears. The absolute number of eosinophils was determined in Levy counting chambers by taking the average count in four dilutions with phloxine propylene glycol diluent (18).

The individuals studied were divided into three groups. Group A consisted of 20 human subjects, including six active and healthy volunteers and 14 hospitalized patients in whom no physical or significant mental illness could be demonstrated. Group B comprised 11 hospitalized patients who had been admitted with various illnesses of a purely medical nature, and who, on recovery, were studied just prior to discharge from the hospital. Group C included three patients in whom a simple but significant inflammatory (neutrophilic) leucocytosis existed at the time of the test. One patient was receiving penicillin therapy for primary lues, one had sustained minor surgery 24 hours before the test, and one patient had an active inflammatory process associated with pyoderma. Control studies following the injection of 1 ml. of water were carried out in three subjects to determine whether the procedure of injection and ten to 12 venipunctures produces any significant cell changes.

RESULTS

A biphasic alteration in the number of circulating leucocytes followed the injection of epinephrine in all 34 instances (Figure 1). Phase I consisted of a prompt mobilization of all white cell elements, which appeared within five minutes. The maximal effect occurred at 17 minutes, and thereafter subsided toward normal. The average maximal total white cell count was 11,625 per c. mm., an increase of 75 per cent above the average pre-injection count of 6,626 per c. mm. (Table I). The average maximal neutrophil count at the height of the epinephrine effect was 5,550 per c. mm., an increase of 45 per cent above the average baseline neutrophil count of 3,825 per c. mm. The average lymphocyte count at the maximal point was 5,175 per c. mm., an increase of 130 per cent above the control value of 2,250 per c. mm. The average number of circulating eosinophils, at the height of the effect of the stimulus, was 203 per c. mm., an increase of 45 per cent above the pre-injection average count of 138 per c. mm. It will

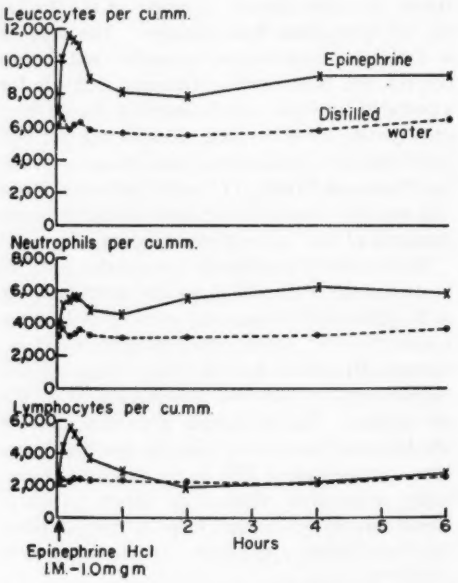

FIG. 2. THE INFLUENCE OF EPINEPHRINE HYDROCHLORIDE COMPARED WITH DISTILLED WATER ON CIRCULATING LEUCOCYTES IN THE SAME THREE NORMAL HUMAN SUBJECTS

TABLE I

The mean leucocyte count at rest in 20 normal human subjects and the change in cell count following the intramuscular injection of epinephrine (Group A)

Cells	Phase	Mean count *per c.mm.*	Standard error	Range	Mean change *per cent*	P*
Total leucocytes	Control	6,625	±250	4,300 8,900		
	I—(17 min.)	11,625	±700	6,420 17,000	+ 75.5	<0.001
	II—(4 hours)	9,700	±475	5,820 14,825	+ 46.4	<0.001
Neutrophils	Control	3,825	±200	1,975 5,075		
	I—(17 min.)	5,550	±425	2,250 9,350	+ 44.8	<0.001
	II—(4 hours)	7,075	±375	4,365 10,800	+ 84.9	<0.001
Lymphocytes	Control	2,250	±150	1,400 3,350		
	I—(17 min.)	5,175	±375	2,750 8,000	+130.0	<0.001
	II—(2 hours)	1,925	±125	1,150 3,650	− 14.9	< .01
Eosinophils	Control	138	± 10	47 285		
	I—(17 min.)	203	± 20	68 444	+ 47.0	<0.001
	II—(4 hours)	80	± 5	30 153	− 42.1	<0.001

* P—The probability that the given per cent change is not different from a mean change of zero. The probability that the change is statistically significant is therefore high in every instance.

be seen in Table I that all changes are highly significant, P values being less than 0.01 in all instances.

There was a tendency for the number of circulating lymphocytes to equal the number of neutrophils at the height of the effect in Phase I, despite the fact that normally the absolute number of lymphocytes is less than two-thirds of the resting neutrophil count (L–2,250, N–3,825). The degree of change in the lymphocytes was, therefore, greater than observed in the other white cell elements. The lymphocytes in Phase I were usually mobilized at the same time as were neutrophils although, in several instances, the lymphocytosis preceded the neutrophilia. It is noteworthy that the eosinophils, although small in absolute numbers, were increased significantly in the first phase following the injection of epinephrine.

The changes related to Phase II (Figure 1) became apparent within two hours after the administration of epinephrine. At this time the lymphocytes were observed to be maximally altered from control levels by a decrease of 15 per cent (Table I). Changes in the number of circulating neutrophils were maximal at four hours, at which time an increase of 85 per cent above control values was recorded. It is obvious that the secondary elevation of the neutrophil count is responsible for the overall 46 per cent increase in the total white cell count observed at four hours. Eosinophil changes were characterized by a decrease of 42 per cent below pre-injection values, the maximal effect also occurring at four hours.

As illustrated in Figure 2 the injection of 1.0 ml. of distilled water followed by repeated venipuncture failed to cause significant alterations in the

number of circulating leucocytes throughout a six hour period of observation. The administration of epinephrine to the same three individuals was followed by the characteristic biphasic leucocyte response.

Eleven patients (Group B) who were hospitalized for a variety of medical illnesses (Table II) were "epinephrine-tested" just prior to discharge from hospital. The cellular response to epinephrine was the same as in Group A except that in this group the neutrophilia expected during Phase II was significantly less, an average increase of 54 per cent being recorded as compared with 85 per cent in the normal subjects. A manifestation of the same phenomenon, but to an even greater degree, was observed in three patients (Group C) who, at the time of the test, had a leucocytosis associated with acute inflammation. In all three instances in Group C, (Table II) the number of circulating neutrophils, at the height of the effect in Phase II, was found to be actually reduced below pre-injection levels (− 27 per cent) rather than having reached the expected 85 per cent increase. The difference between the three groups, in regard to the secondary neutrophilic response is statistically highly significant (Table III).

DISCUSSION

In normal human subjects all components of the circulating white cell series are mobilized in the "primary phase" (Phase I) of the epinephrine test. This observation is clinically significant inasmuch as a similar change in circulating leucocytes is implied by some authors (7, 8) to represent the degree of sequestering activity of the spleen. It is further implied by those authors that an increase beyond the normal degree of response in the mobilization of circulating leucocytes following epinephrine administration would reflect an increased, pathologic sequestering activity of a hyperactive spleen.

Admittedly the clinically enlarged spleen does commonly decrease in size following parenteral administration of epinephrine concomitantly with

TABLE II

Maximal per cent change in the number of circulating leucocytes occurring within Phase I and Phase II after the intramuscular injection of epinephrine in patients hospitalized for various medical illnesses (Group B) and in patients with inflammatory leucocytosis (Group C)

Group B	Total white cell count		Neutrophils		Lymphocytes		Eosinophils		Diagnosis
Phase	I	II	I	II	I	II	I	II	
Case 1	+ 24	+ 9	+ 31	+16	+ 19	−12	+ 27	− 6	Acute anxiety
2	+ 48	+27	+ 25	+36	+ 90	−23	+ 42	−38	Acute peptic ulcer
3	+ 43	+56	+ 30	+96	+ 96	−22	0	−64	Friedreich's ataxia
4	+ 84	+46	+ 47	+57	+120	+35	+ 90	− 3	Epidermophytosis
5	+ 90	+30	+ 45	+80	+210	−55	+ 40	−70	Acute B. dysentery
6	+ 34	+20	+ 19	+37	+145	−30	+ 70	−40	Ess. hypertension
7	+ 79	+46	+ 71	+76	+ 89	−50	+ 96	+ 2	Ess. hypertension
8	+154	+42	+108	+73	+300	0	+393	−44	Hypertension Nephrectomy
9	+ 86	+20	+ 45	+23	+165	− 6	+105	− 7	Chronic congestive failure
10	+ 92	+32	+ 57	+45	+245	+10	+ 22	−29	Renal hypertension
11	+ 84	+44	+ 68	+55	+155	−40	+ 78	−38	Renal hypertension
Mean	+ 74	+34	+ 50	+54	+150	−23	+ 88	−31	

Group C	Total white cell count		Neutrophils		Lymphocytes		Eosinophils		Diagnosis
Phase	I	II	I	II	I	II	I	II	
Case 1	+49	−17	+25	−16	+100	−51	+50	−53	Minor surgery
2	+48	−22	+13	−29	+112	− 9	+20	−17	Acute pyoderma
3	+54	−29	+27	−36	+110	−25	+64	−40	Primary chancre
Mean	+50	−23	+22	−27	+107	−28	+45	−37	

TABLE III

The mean maximal per cent change in the number of circulating leucocytes occurring within Phase I and Phase II after the intramuscular injection of epinephrine hydrochloride in hospital patients

Group	No.	Total white count		Neutrophils		Lymphocytes		Eosinophils	
		Phase I	Phase II	Phase I	Phase II	Phase I	Phase II	Phase I	Phase II
A*	20	+89	+60	+59	+108	+166	−16	+77	−46
B†	11	+74	+34	+50	+ 54	+150	−23	+88	−31
C‡	3	+50	−23	+22	− 27	+107	−28	+45	−37
PB§					<0.01				
PC‖					<0.05 >0.01				

* Group A—Normal human subjects.
† Group B—Patients hospitalized for various acute and chronic illnesses.
‡ Group C—Patients with acute inflammatory neutrophilic leucocytosis.
§ PB—The difference in the response of neutrophils of Group B in Phase II as compared with Group A is highly significant.
‖ PC—The difference in the response of neutrophils of Group C in Phase II as compared with Group B is significant. Compared with Group A then the difference is highly significant.

the increase in circulating leucocytes (19). It appears, however, that complex mechanisms other than splenic contraction are involved in Phase I leucocyte changes (20).

From these observations concerning Phase I it may be concluded that the application of the epinephrine test in the recognition of "hypersplenic" states requires consideration of the degree of response in normal human subjects. A comparison between the response in normal subjects and patients with hematologic changes characteristic of the "hypersplenic" syndromes is at present in preparation.

Michael (13), in an extensive review has recently considered the biphasic alterations in the circulating leucocytes which follow the administration of epinephrine. He has suggested that a hormonal influence of the pituitary-adrenocortical system may be involved in the primary changes in circulating leucocytes which follow the injection of epinephrine. It is of interest that the administration of ACTH [3] to two subjects in this laboratory failed to evoke significant primary changes in either instance.

Hormonal factors do seem concerned, however, in the leucocyte changes of Phase II. That an increase in circulating neutrophils, together with a decrease in lymphocytes and eosinophils, reflects an increased adrenal cortical secretion is well documented (9, 21, 22). Identical changes follow the injection of ACTH in both animals and man. These leucocyte changes, therefore, reflect augmented activity of the intact pituitary-adrenocortical system.

It has been previously demonstrated that the administration of epinephrine in normal human subjects also elicits the general leucocyte changes characteristic of Phase II herein described (9, 12). In experimental animals the removal of the anterior pituitary gland or the adrenal cortex, however, vitiates the secondary lymphopenia and eosinopenic response to epinephrine (9). In human subjects during states of hypoadrenal activity, the secondary eosinopenic response to epinephrine has been shown to be absent (11).

Neutrophils, on the other hand, demonstrate a quite dissimilar behavior. Dougherty and White (21) clearly demonstrated that despite removal of the adrenal cortex in experimental animals, an increase in circulating neutrophils nonetheless followed the administration of ACTH. In these instances the lymphopenia did not appear. Hills, Forsham and Finch (23) described a similar although submaximal neutrophilia following the administration of ACTH in patients with Addison's disease. During these tests lymphopenia and

[3] ACTH—A single intramuscular injection of ACTH, equivalent in potency to 25 mg. of the Armour Standard La-1-A, supplied through the courtesy of Dr. J. R. Mote, Armour Laboratories, Chicago, Ill.

eosinopenia did not occur. More recently Hungerford (24) has reported that despite simultaneous hypophysectomy and adrenalectomy in rats, the injection of adrenalin is followed by a significant increase in the number of circulating neutrophils at four hours.

It therefore appears that the presence of the anterior pituitary gland or adrenal cortex is not essential for the secondary neutrophilic response to epinephrine and ACTH, unlike the behavior of lymphocytes and eosinophils. Factors which influence the number of circulating neutrophils are not therefore identical with those responsible for changes in circulating lymphocytes and eosinophils. This is in keeping with our observation of an unexpected decrease in circulating neutrophils in Phase II despite the normal lymphopenic and eosinopenic response to epinephrine in the patients with inflammatory leucocytosis (Group C).

The injection of epinephrine in normal human subjects is thus characterized by a biphasic alteration in the number of circulating leucocytes. The primary phase involves a mobilization of at least neutrophils, lymphocytes and eosinophils. In an analysis of secondary changes the early primary alterations may certainly influence the degree of response in the later phase. It would seem, therefore, that frequent sampling of blood is necessary to delineate the quality and quantity of leucocyte changes in both phases of the epinephrine test.

SUMMARY

1. Epinephrine (1.0 mg.) was administered intramuscularly to 34 human subjects. A biphasic alteration in the number of circulating leucocytes was observed.

2. In Phase I a prompt mobilization of all white cell elements appeared within five minutes, the effect became maximal at 17 minutes, and thereafter returned toward normal. The total white cell count increased 75 per cent, the neutrophils increased 45 per cent, the lymphocytes 130 per cent, and the eosinophils 47 per cent at the time of maximum change.

3. The second phase consisted of a secondary rise in the total white cell count of 46 per cent, an 85 per cent increase in circulating neutrophils, a 15 per cent reduction in lymphocytes and a 42 per cent decrease in eosinophils. The maximal effect on the lymphocytes was apparent at two hours after injection, while the changes in total white cell count, neutrophils and eosinophils were maximal at the four hour sampling.

4. In three patients with a neutrophilic leucocytosis associated with acute inflammation there was a reduction (-27 per cent) in the number of circulating neutrophils at four hours after the injection of epinephrine.

5. The mechanisms involved in both phases and the limitations in the clinical application of the epinephrine test are discussed briefly.

ACKNOWLEDGMENTS

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THE EFFECT OF INTRAVENOUS INFUSION OF THROMBOPLASTIN ON "HEPARIN TOLERANCE" [1]

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The widespread use of anticoagulants in the prophylaxis and therapy of thrombo-embolic disease has stimulated interest in methods for selecting patients who are predisposed to intravascular clotting. It has been suggested but by no means proved that inherent hypercoagulability of the blood is a frequent factor in the pathogenesis of thrombosis. On the basis of this belief several clinical tests have been devised to detect hypercoagulability of the blood. Increased resistance to the anticoagulant activity of heparin has been reported to occur in patients with thrombotic disease. The clotting time of blood drawn following intravenous injection of heparin was said to be shorter in patients predisposed to thrombosis than in normal individuals receiving the same amount of heparin (1, 2). Similar results were obtained with blood heparinized *in vitro* (3). Increased resistance to heparin has been attributed to the liberation of thromboplastin into the blood following surgical operations and in certain other conditions in which thromboses frequently occur (3–5).

Thromboplastic substances accelerate the coagulation of blood and can overcome the anticoagulant effect of heparin *in vitro* (6). However, no evidence is available to support the belief that thromboplastin liberated into the circulating blood can cause an increased resistance to the anticoagulant action of heparin. The effect of the intravenous injection of thromboplastin on "heparin tolerance" was therefore studied. Experiments were performed in which dogs were given intravenous infusions of homologous brain thromboplastin. "Heparin tolerance" was measured repeatedly before, during, and after the infusions. In no instance was increased resistance to heparin noted. Administration of small amounts of thromboplastin resulted in exaggerated response to heparin, and larger amounts delayed the coagulation of blood.

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[2] Postdoctorate Fellow, U. S. Public Health Service.

METHODS AND MATERIALS

Healthy mongrel dogs weighing 7.3 to 13.6 kilograms were anesthetized by the intravenous injection of sodium pentobarbital, and anesthesia was maintained for three to six and one-half hours by repeated injections of the drug as necessary. A thromboplastin preparation was infused from a calibrated buret through a 20 gauge needle into a saphenous vein. Blood was drawn from the jugular veins using 20 gauge needles and silicone-treated syringes. At intervals before, during, and after the infusion of thromboplastin, specimens were obtained for clotting studies.

Preparation of thromboplastin. Thromboplastin was prepared from acetone-extracted dog brain by the method of Brambel (7). The resulting suspension was centrifuged in a Servall angle centrifuge at 11,500 r.p.m. for 10 minutes to remove particulate material. The slightly opalescent supernatant fluid contained from 6 to 12 mg. of brain solids per ml. as measured by drying *in vacuo*. The thromboplastic activity of this material was determined by testing its clot-accelerating effect on the plasma of the dog to be infused with the preparation. One-tenth ml. of thromboplastin was added to 0.1 ml. of oxalated plasma. This mixture was clotted at 37° C. by the addition of 0.1 ml. of M/40 calcium chloride solution. Various thromboplastin preparations clotted dog plasma in eight to 13 seconds. For intravenous use the thromboplastin was appropriately diluted with 0.85% saline solution and filtered through glass wool into the infusion apparatus. The thromboplastic activity of the diluted and filtered material was then determined as described above.

Clotting times. Clotting times were determined at 37° C., employing 1 ml. portions of blood in acid-washed 13 × 100 mm. Pyrex test tubes. Two tubes were used for each determination. The clotting time of the blood of normal dogs varied between 10 and 20 minutes, values essentially identical with those obtained in human subjects with the same technique.

In vitro "heparin tolerance." One ml. portions of freshly drawn blood were placed in Pyrex clotting tubes

containing 0.1 ml. of heparin[3] solution. The final concentration of heparin was varied from 0.05 to 0.2 Toronto units per ml. of blood. The clot-retarding effect of the various heparin concentrations was determined by comparing the clotting time of heparinized and unheparinized blood. Each test was carried out in duplicate at 37° C. At least two control "heparin tolerance" tests were performed on each animal.

In vivo "heparin tolerance." After several control clotting times were performed, a measured volume of heparin solution was injected into a saphenous vein. The clotting time of blood drawn from the jugular vein was determined at intervals following the injection.

Prothrombin times. To freshly drawn blood was added 10% by volume of M/10 sodium oxalate solution. The prothrombin content of oxalated plasma was estimated by the one-stage method employing rabbit brain thromboplastin prepared by the technique of Brambel (7). In addition the prothrombin time of plasma diluted to 12½% was determined. The diluent employed was 0.85% sodium chloride solution or a solution containing six parts of saline and one part of M/10 sodium oxalate solution. In some experiments in which saline alone was used, diluted plasma clotted prior to the addition of calcium chloride solution. Prothrombin times on 12½% plasma were performed at least in triplicate.

Fibrinogen determinations. The fibrinogen concentration of oxalated plasma was determined by the method of Ratnoff and Menzie (8).

Platelet counts. Platelet counts were performed in duplicate by a direct method employing Rees-Ecker diluent.

Thrombin clotting times. The time necessary for clot formation after the addition of 0.2 ml. of a thrombin[4] solution to an equal volume of oxalated plasma was determined in duplicate at 37° C. Powdered thrombin was dissolved in barbital buffer to a concentration of 2.0 units per ml.

Barbital buffer. Barbital buffer was prepared from the following substances: sodium diethylbarbiturate 2.06 grams, diethylbarbituric acid 2.76 grams, sodium chloride 7.30 grams, and sufficient triple-distilled water to bring the total volume to one liter. To facilitate solution the mixture was heated gently without boiling. The pH of this solution was 7.5 ± 0.1.

EXPERIMENTAL STUDY

Normal dogs, anesthetized with nembutal, were given intravenous infusions of homologous brain thromboplastin. The thromboplastic activity of the preparations and the rate of infusion were varied over wide ranges. Animals receiving these infusions showed no evidence of untoward reactions except in those instances in which rapid injections of very potent thromboplastin were given. Pulse and respirations did not appear to be influenced by the infusions. No convulsive movements were noted. In no instance was there detectable thrombosis of the saphenous vein at the site of the thromboplastin infusion. Recovery from anesthesia was uncomplicated, and the animals appeared normal for a period of observation of at least one week. No animals were sacrificed.

When an injection of 10 ml. of a potent thromboplastin[5] was given within 30 seconds, the animal appeared to be in respiratory distress for about 15 minutes. Thereafter, recovery was prompt and uncomplicated. The administration of 10 ml. of even more potent thromboplastin (prothrombin time 13 seconds or less) within 30 seconds was followed by evidence of severe respiratory distress and death within two or three minutes. At autopsy large clots were found in the chambers of the right side of the heart, pulmonary arteries, and frequently in the inferior vena cava.

In vitro "heparin tolerance." Figure 1 gives the results of a typical experiment. This experiment will be described in detail:

A healthy 10 kilogram male mongrel dog was anesthetized by the intravenous injection of sodium pentobarbital, 30 mg. per kilogram. Anesthesia was maintained for about three hours by two subsequent injections of 25 mg. of the drug. Seventeen ml. of blood were obtained by jugular vein puncture with a 20 gauge needle and a 20 ml. silicone-treated syringe. This blood was used for *in vitro* "heparin tolerance" tests, prothrombin and thrombin clotting times, and platelet, hematocrit, and fibrinogen determinations. Five and 28 minutes later other blood specimens were obtained and these tests repeated. Thus, three separate control determinations were made before the beginning of the thromboplastin infusion. One minute after the last control specimen had been drawn, an infusion of dog brain thromboplastin was started in the left saphenous vein through a 20 gauge needle. This particular preparation of dog brain thromboplastin contained 0.64 mg. of brain solids per ml. The thromboplastic activity of the material was such that it gave a prothrombin time of 18 seconds with the dog's plasma. The infusion was maintained at a rate of 0.75 ml. per minute for a period of eight minutes at which time another specimen of blood was obtained for study.

The infusion was continued at the following rates during each successive period: 1.0 ml. per minute for nine

[3] Heparin sodium was kindly supplied by the Upjohn Company, Kalamazoo, Michigan.

[4] Thrombin (bovine) was obtained through the courtesy of the Upjohn Company, Kalamazoo, Michigan.

[5] The thromboplastin gave a prothrombin time of 22 seconds with the dog's plasma.

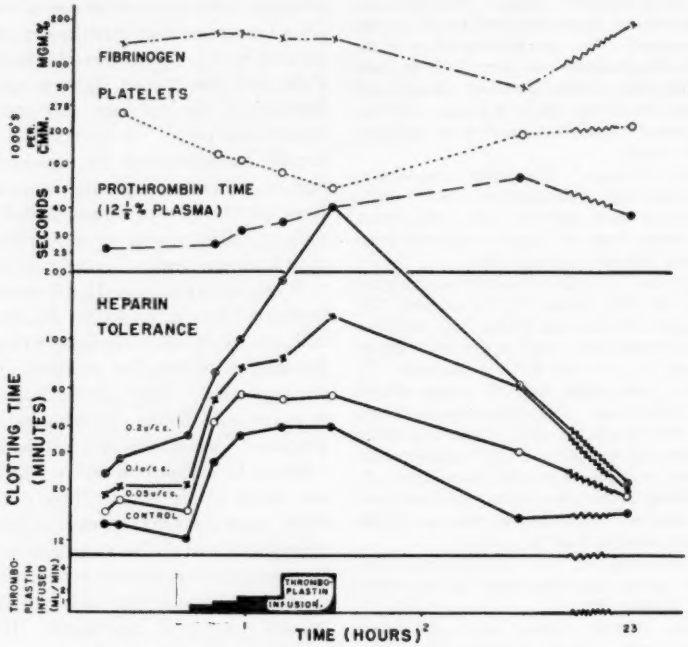

FIG. 1. EFFECT OF THROMBOPLASTIN INFUSION ON HEPARIN TOLERANCE

minutes, 1.5 ml. per minute for 14 minutes, and 3.2 ml. per minute for 18 minutes. At the end of each period blood specimens were obtained for clotting studies. The total time required for the administration of thromboplastin was 49 minutes. Blood drawn during the infusion did not clot after the addition of oxalate, indicating that thrombin was not present in the blood obtained from the jugular vein. One and 23 hours after the infusion was discontinued, additional specimens were obtained.

The animal withstood the procedure well. Pulse and respirations remained normal, and at no time was there evidence of distress. Recovery from anethesia was uncomplicated, and the dog appeared normal for the period of observation of one week following the procedure.

In this experiment the infusion of thromboplastin resulted in prolongation of the clotting time, exaggerated response to heparin, prolongation of the prothrombin times of undiluted and 12½% plasma, and decrease in platelets. These changes could not be accounted for on the basis of alteration in fibrinogen concentration. The hematocrit values did not change appreciably.

It was apparent that the infusion of the material used in this experiment did not increase heparin resistance but actually led to the development of a severe coagulation defect. Therefore, in other experiments thromboplastin preparations of lower activity were employed. In one experiment the thromboplastic activity of the material infused was such that it gave a prothrombin time of 30 seconds with the dog's plasma. Eighty and one-half ml. of this preparation were given at increasing rates over a period of 66 minutes. There was slight prolongation of the clotting time, exaggerated response to heparin, increase in the prothrombin time of 12½% plasma, and decrease in platelets. At no time was a reduction of the fibrinogen concentration detected.

When the amount of thromboplastin infused was further decreased, the effects on the coagulation mechanism were much less striking. An experiment was performed in which 31 ml. of a brain preparation were infused over a period of 33 minutes. This thromboplastin gave a prothrombin time of 27 seconds with the dog's plasma. The results were similar to those obtained in the

previous experiments except that the changes were slight and of questionable significance.

In another experiment the effects of a prolonged infusion of very weak thromboplastin preparation were studied. This thromboplastin gave a prothrombin time of 61 seconds with the dog's plasma.[6] A total of 89 ml. was given over a period of 124 minutes at an average rate of infusion of 0.72 ml. per minute. There was no evidence of hypercoagulability of the blood or of increased resistance to heparin. The slight changes which occurred suggested a mild impairment of coagulation.

Since it was not possible to demonstrate hypercoagulability of the blood during the infusion of relatively weak thromboplastin, attempts were made to produce temporary states of hypercoagulability by the injection of very potent material. One dog received an infusion of 28 ml. of a thromboplastin which gave a prothrombin time of 12 seconds with the dog's plasma. This material contained 6.9 mg. of brain solids per ml. The infusion was given over a period of 52 minutes. All of the changes depicted in Figure 1 were also seen in this experiment, but were more marked. However, the animal withstood the infusion without evidence of disability.

In other experiments potent thromboplastin was injected at a rapid rate from a syringe. Table I summarizes the results of an experiment of this type. Ten ml. of a preparation which gave a prothrombin time of 22 seconds with the dog's plasma were injected within a period of 30 seconds. This material contained 2.3 mg. of brain solids per ml. Blood drawn one minute after the injection showed slight prolongation of the clotting time and a greatly exaggerated response to heparin. The clotting time quickly returned to normal, but marked sensitivity to heparin persisted. No significant change occurred in the prothrombin times. There was no reduction of the fibrinogen concentration. The platelet count fell precipitously but returned to normal within 33 minutes. There was no external evidence of intravascular clotting, and the animal appeared to suffer no adverse effects from this injection. Thirty-four minutes after the first injection, 10 ml. of a preparation which gave a prothrombin time of 13 seconds were injected within 30 seconds. This amount of brain extract caused immediate death in animals which had not received a prior injection of less concentrated material. Although the respiratory rate increased from 12 to 35 per minute and respirations appeared labored for about 15 minutes after the injection, the animal survived the procedure without further difficulty. Recovery from anesthesia was uneventful, and the dog was normal in behavior and appearance for the period of observation of one week.

[6] The feeble activity of this thromboplastin was indicated by the fact that this dog's plasma clotted in 90 seconds when 0.85% saline solution was substituted for the thromboplastin preparation.

TABLE I

Effects of rapid intravenous injection of thromboplastin

Time in relation to thromboplastin injection	Clotting times of 1.0 ml. portions of blood containing the following concentrations of heparin (units per ml. of blood)				Prothrombin time		Fibrinogen	Platelets
	0	0.10	0.15	0.20	Undiluted plasma	12½% plasma		
	min.	*min.*	*min.*	*min.*	*sec.*	*sec.*	*mg. %*	*per cmm.*
61 minutes before	16	24	27	—	—	—	234	300,000
58 minutes before	16	24	34	—	—	—	264	283,000
26 minutes before	11	23	26	75	8	30	—	—
Thromboplastin* 10 ml. injected within 30 seconds								
1 minute after	20	220	270	>420	9	32	274	96,000
3 minutes after	17	50	240	>420	9	33	366	102,000
5 minutes after	14	25	110	>420	8	33	254	107,000
33 minutes after	13	74	190	210	8	33	397	287,000

* This material gave a prothrombin time of 22 seconds with the dog's plasma.

The rapid injection of 10 ml. of potent thromboplastin killed the animals unless they had been rendered refractory by previous injection of diluted thromboplastin. When dogs were given rapid intravenous injections of 10 ml. of very potent thromboplastin, there was immediate profound respiratory distress and death followed within several minutes. Blood drawn within 30 to 60 seconds following the injection clotted before ejection from the syringe. Clots formed even when the blood was oxalated, indicating the presence of thrombin. In some experiments the rapid injection of sublethal amounts of thromboplastin was followed by evidence of thrombin activity in the blood drawn within a few seconds after the injection. However, blood drawn one minute or more after the termination of the thromboplastin injection no longer showed the presence of thrombin.

In vivo "heparin tolerance." The effect of infusion of thromboplastin on the response to intravenous heparin is shown in Figure 2.

A healthy 7.3 kilogram mongrel female dog, anesthetized with nembutal, was given an injection of 0.9 ml. of a heparin solution containing 100 units per ml. into the saphenous vein. Blood for clotting studies was drawn before the injection and two, five, 10, 20, and 30 minutes thereafter. After the clotting time had returned to normal, an intravenous infusion of 31 ml. of thromboplastin was started in the contralateral saphenous vein. The thromboplastic activity of this material was such that it gave a prothrombin time of 30 seconds with the dog's plasma. The infusion was continued for a period of 40 minutes at an average rate of 0.75 ml. per minute. Five minutes after the infusion was started, another specimen of blood was obtained for clotting studies. Then a second injection of the same amount of heparin which had been previously employed was given. Specimens for clotting studies were obtained at the same intervals as after the control injection of heparin.

There was no increase in resistance to the anticoagulant activity of the injected heparin during

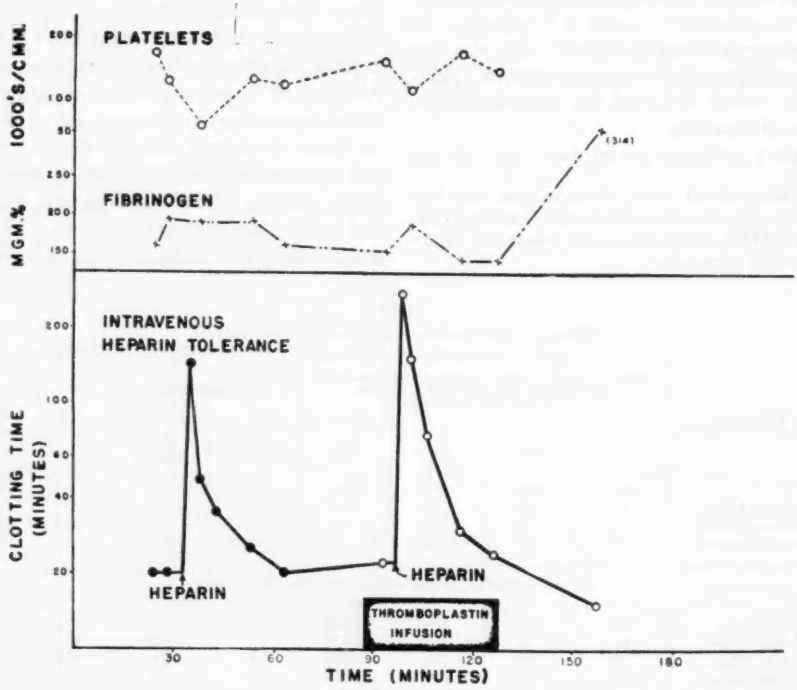

FIG. 2. EFFECT OF THROMBOPLASTIN INFUSION ON *IN VIVO* HEPARIN TOLERANCE

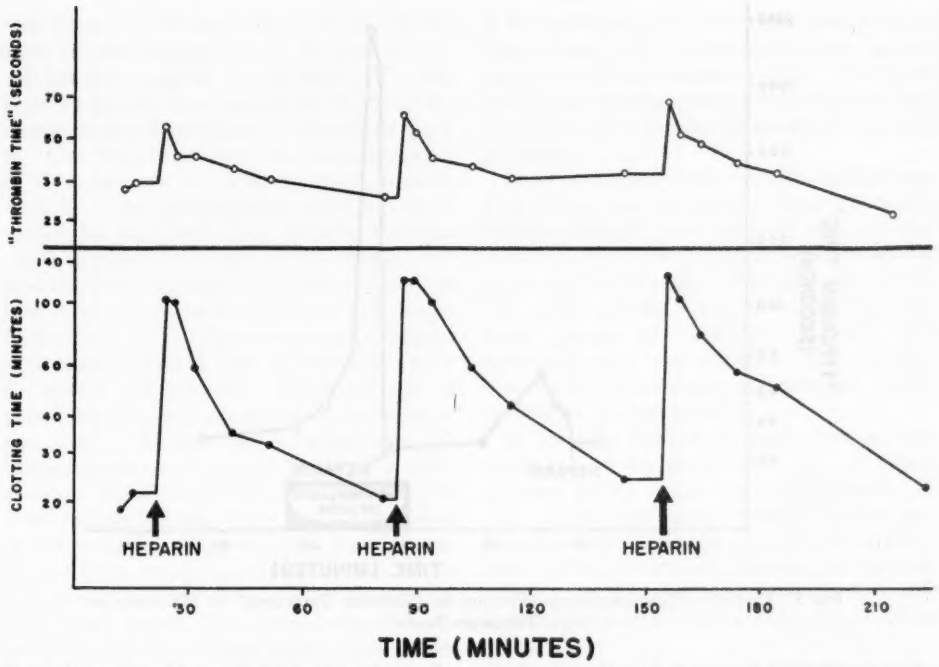

FIG. 3. EFFECT OF REPEATED INJECTIONS OF HEPARIN ON CLOTTING AND "THROMBIN" TIMES

the infusion of thromboplastin. In fact, the clotting times were longer than after the control injection of heparin. No significant change in fibrinogen levels occurred until the end of the experiment, at which time there was an increase. The platelet count fell after the control injection of heparin, but the fall was not appreciable when heparin was injected during the thromboplastin infusion. In a control experiment, repeated intravenous "heparin tolerance" tests were performed

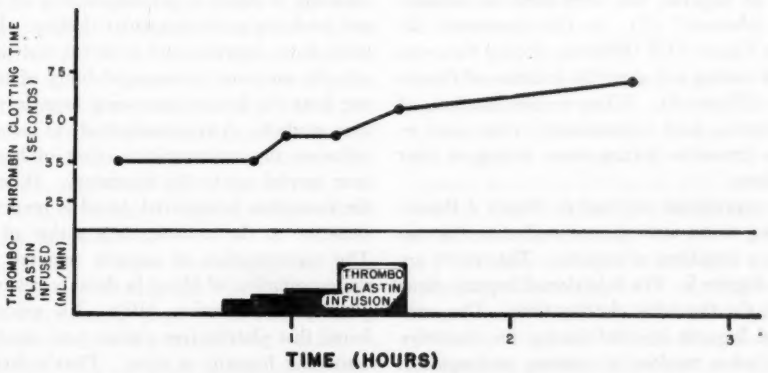

FIG. 4. EFFECT OF THROMBOPLASTIN INFUSION ON "THROMBIN TIME"

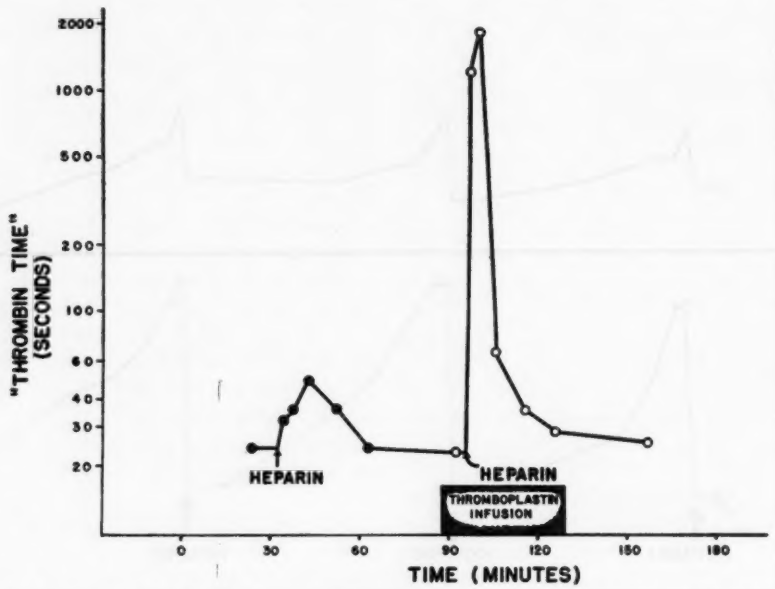

FIG. 5. EFFECT OF THROMBOPLASTIN INFUSION ON "HEPARIN TOLERANCE" AS MEASURED BY "THROMBIN TIMES"

on an anesthetized dog to which no thromboplastin was administered. Results of this experiment, shown in Figure 3, demonstrate the reproducibility of the "heparin tolerance" test under these conditions.

"Heparin tolerance" as measured by the thrombin clotting time. The thrombin clotting time of oxalated plasma, obtained after the intravenous injection of heparin, has been used to measure "heparin tolerance" (9). In the experiment described in Figure 1 the thrombin clotting time was prolonged during and after the infusion of thromboplastin (Figure 4). When smaller amounts of thromboplastin were administered, there was no change in thrombin clotting times during or after the infusions.

In the experiment depicted in Figure 2 thrombin clotting times were determined after the two intravenous injections of heparin. The results are shown in Figure 5. The injection of heparin alone prolonged the thrombin clotting time. The same amount of heparin injected during the thromboplastin infusion resulted in extreme prolongation. That this prolongation was not due to the additive effects of repeated injections of heparin is shown in a control experiment (Figure 3). Thus the infusion of thromboplastin produced no increase in resistance to heparin as measured by the thrombin clotting time.

DISCUSSION

"Heparin tolerance" tests have been employed clinically to detect hypercoagulability of the blood and tendency to intravascular clotting. However, there is no experimental evidence that these tests actually measure hypercoagulability of the blood, nor have the factors increasing heparin resistance been studied. A systematic study of factors which influence the anticoagulant effect of heparin has been carried out in this laboratory. When thrombin formation is impaired, blood is rendered more sensitive to the anticoagulant action of heparin. The concentration of heparin required to delay the coagulation of blood is directly related to the platelet concentration (10). No evidence was found that platelet-free plasma was capable of inactivating heparin *in vitro*. Platelet-free plasma from normal subjects as well as from patients

with thrombotic or hemorrhagic disease did not affect the anticoagulant activity of heparin (11).

It has been suggested that liberation of thromboplastin into the blood may render the blood hypercoagulable and predispose to thrombosis (3, 4, 9). The "heparin tolerance" test has been thought to be a measure of circulating thromboplastin (3–5, 9). The experiments described provide no support for this belief. Dogs receiving thromboplastin infusions, with the rate of infusion and thromboplastic activity of the material varied over wide ranges, displayed no evidence of hypercoagulability of the blood. On the contrary a coagulation defect associated with increased sensitivity to heparin was observed. Rapid injection of potent thromboplastin resulted in the formation of gross clots in the right side of the heart and pulmonary arteries, and death of the animal in a few minutes. Blood drawn from these animals within a few seconds following the injection clotted even though oxalated, suggesting that thrombin was present in the circulating blood. In some similar experiments in which the animal survived, oxalated blood clotted. This phenomenon was observed only in blood drawn within a few seconds after the rapid injection of potent thromboplastin.

When large amounts of thromboplastin were infused, there was a reduction of the plasma fibrinogen concentration. Complete removal of fibrinogen can be accomplished *in vivo* by thromboplastin infusion (12, 13). When smaller amounts were administered so that the fibrinogen level was not appreciably altered, a severe coagulation defect was nevertheless produced. This defect was characterized by increased sensitivity to the anticoagulant action of heparin, prolongation of the clotting time, decrease in the platelet count, prolongation of the prothrombin time and in particular the prothrombin time of diluted plasma, and delayed coagulation of plasma by thrombin. The degree of the coagulation defect was related to the amount of thromboplastin administered and the rate of the infusion.

The nature of this peculiar coagulation defect is not completely understood. Thrombin formation was undoubtedly impaired by the reduction in the concentration of platelets and possibly in prothrombin. However, the prolonged thrombin clotting time cannot be explained on this basis. It has previously been shown that the plasma of dogs infused with thromboplastin may acquire thrombin-inhibitory properties (13). The degree of thrombocytopenia produced was not adequate to account for the increased sensitivity of the blood to heparin.

Some investigators have noted that animals may be protected from an otherwise lethal injection of thromboplastin by prior injection of a sublethal dose. This refractory phase has been attributed to the removal of fibrinogen by the first injection (12, 14). The protective action of a preliminary sublethal injection was confirmed. However, it is noteworthy that this refractory state occurred even though the fibrinogen concentration was not reduced by the first injection.

It has been thought by some observers that shortening of the prothrombin time of diluted plasma is an index of tendency to thrombosis (15, 16). In the experiments recorded here the prothrombin times of diluted plasma were not shortened by the intravenous infusion of thromboplastin. On the other hand there was frequently a prolongation of the prothrombin time of diluted plasma.

The intravenous injection of heparin resulted in a decrease in platelet concentration (Figure 2). The thrombocytopenia produced by intravenous injections of commercial heparin has been reported by others (17, 18). However, these investigators used larger amounts of heparin than were used in the present experiments. It is of interest that small amounts of heparin also produced transient thrombocytopenia.

SUMMARY

1. The effect of the intravenous infusion of homologous brain thromboplastin on the "heparin tolerance" test was studied in dogs. No increase in resistance to the anticoagulant activity of heparin was noted during the infusion of thromboplastin. On the other hand exaggerated response to heparin was observed.

2. The infusion of thromboplastin resulted in a coagulation defect which was characterized by prolongation of the clotting time, prolongation of the prothrombin time of diluted and undiluted plasma, decrease in platelet concentration, and prolongation of the thrombin clotting time. These effects

occurred before there was a measurable reduction in the fibrinogen concentration.

3. No evidence was found to support the view that the "heparin tolerance" test is a measure of circulating thromboplastin.

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ANOXIA AND HUMAN PULMONARY VASCULAR RESISTANCE[1,2]

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Although it has been recognized for some time that anoxia may result in an elevation of the pressure in the pulmonary artery, the mechanism of this response has not been satisfactorily explained.

Von Euler and Liljestrand (1) in 1946 demonstrated in anesthetized cats that breathing 10% to 11% oxygen in nitrogen caused a rise in pulmonary artery pressure which was not affected by vagotomy or excision of the stellate ganglia, and which they therefore attributed to a direct effect of anoxia on the pulmonary vessels. Although left atrial pressure was sometimes recorded directly (2), no measurements of cardiac output were made, so that the pressor effects of changes in vascular resistance could not be separated conclusively from those due to variations in blood flow.

Motley and his associates (3) in 1947 demonstrated the pulmonary hypertensive effect of anoxia in five unanesthetized human subjects, using the technique of cardiac catheterization. A slight fall in cardiac output occurred simultaneously with the rise in pulmonary arterial pressure and an inverse relationship between the two was suggested. Nevertheless, the two possible mechanisms of (*a*) stasis in the smaller pulmonary vessels associated with a decreased output of the left ventricle, or (*b*) pulmonary arteriolar constriction, could not be segregated except by inference.

Recent reviews (4–6) of the pulmonary circulation in general, have accepted the role of anoxia in the pathogenesis of pulmonary hypertension, and have implied that the mechanism involved is pulmonary vasoconstriction. However, vasoconstriction with an increase in the pressure gradient and resistance to blood flow across the human pulmonary vascular bed has heretofore not been conclusively demonstrated to result from anoxia.

The study of pressure in any closed fluid system requires not only a quantitative knowledge of the flow through the system, but an understanding of the resistance to that flow. In analyzing the resistance to the flow of blood from the pulmonary artery through the lungs to the left ventricle, the factor of left atrial or pulmonary venous pressure must be segregated from pulmonary vascular resistance. Without knowledge of the pulmonary venous or "capillary" pressure, it cannot be determined whether changes in pulmonary arterial pressure, themselves, are due primarily to changes in cardiac output or to variations in pulmonary arteriolar resistance.

In 1948 Hellems and co-workers (7) described a method for determining pulmonary "capillary" pressure in man and have since given adequate proof that this pressure varies with the pulmonary venous pressure (8). When the pulmonary artery pressure, the pulmonary "capillary" pressure, and the cardiac output are determined simultaneously, the pulmonary arteriolar resistance may be calculated (9).

It should be emphasized, as is mentioned by Dexter and his co-workers (10), that the term "arteriolar" resistance is used in the physiological sense, since no vessels having the anatomical characteristics of systemic arterioles are found in the lung, and Miller (11) avoids the word in his book. However, it may be used in the physiological sense to designate small vessels between the large branches of the pulmonary artery and the true pulmonary capillaries.

With the foregoing in mind, it was decided to examine the effect of anoxia upon the pulmonary arteriolar resistance in man.

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[2] This study was supported by Research Contract V1001 M-432, Veterans Administration.

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MATERIAL

A study of the effects of anoxia in the normal pulmonary circulation was the primary purpose of this investigation, although a comparison of results in patients with pulmonary hypertension of various types was thought advisable. A total of 32 patients was studied. Twenty-one were considered to have normal cardiovascular-pulmonary systems; four had left ventricular failure of mild to moderate degree; four, pulmonary hypertension associated with obstructive emphysema; one, cor pulmonale and a large diaphragmatic hernia; one, minimal diffuse pulmonary fibrosis, cause undetermined; one, recently compensated hypertensive cardiovascular disease.

METHOD

The majority of the subjects were studied in the post-absorptive state, sedated by 1½ to 3 grains of seconal. Cardiac catheterization was performed according to the method of Cournand and Ranges (12). A double lumen catheter 125 cm. in length was usually employed so that pulmonary "capillary" pressure and pulmonary arterial pressure could be measured simultaneously. Pulmonary "capillary" pressure was determined by the method of Hellems, Haynes and Dexter (8) from the tip of the catheter, which was advanced into a branch of the pulmonary artery as far as possible so as to occlude the branch and transmit pressure distal to the point of occlusion. Pulmonary arterial pressure was recorded from the second lumen which terminated in a side aperture 10 cm. proximal to the catheter tip. The Hathaway blood pressure recording apparatus and Hathaway variable impedance gauges were employed. These latter were connected to the catheter and the indwelling arterial needle by means of two three-way stopcocks, one of which was turned into a drip bottle containing 5% glucose and 20 mg. of heparin per liter whenever pressure recordings or blood samples were not being taken. The second three-way stopcock was opened to atmospheric pressure to establish a base line at the end of each pressure recording, and was used in exhausting air bubbles from the system when connecting the pressure gauges initially. In most instances, electrocardiograms, ballistocardiograms, brachial arterial, pulmonary arterial, and pulmonary "capillary" pressures were recorded simultaneously by means of a five channel optical oscillograph.

Multiple cardiac output determinations were made in 13 of the subjects by the direct Fick method. Two minute samples of expired air were collected in Douglas bags, analyzed for oxygen and CO_2 in the Haldane apparatus, and measured in a Tissot spirometer. Duplicate samples were required to check within 0.03%.

As will be noted in Table I, the resting ventilation and oxygen consumption values occasionally appeared to be lower than expected. This was attributed to the degree of sedation accomplished by the pre-medication described, and was reflected in the control arterial oxygen saturations, which averaged 93.1%, also slightly below accepted normal values.

Pulmonary artery and brachial artery blood samples of 10–12 cc. each were obtained simultaneously over a period of 45 to 60 seconds during the collection of expired air, and were analyzed for CO_2 and oxygen in the Van Slyke manometric apparatus. Duplicate analyses were required to check within 0.2 volume per cent.

Control pressure tracings and cardiac output determinations were obtained usually after the catheter and indwelling arterial needle had been in place for 15 to 30 minutes or more. The rubber mouthpiece and attached flutter valve for air collection and gas breathing was inserted before control pressures were recorded. By means of a three-way respiratory stopcock attached to the valve and mouthpiece, the subjects were then caused to inspire from an anesthesia bag kept partially filled at all times by adjustment of a direct connection to a pressure tank containing 13% oxygen in nitrogen. Expiration was to the outside, and could be diverted to the Douglas bags for sampling by means of a second three-way respiratory stopcock.

The effect of the low oxygen breathing on the pulmonary artery pressure was observed on a cathode ray oscilloscope incorporated in the Hathaway pressure recording apparatus, and permanent records were made at frequent intervals. When a maximum sustained effect on the pulmonary artery pressure had been observed, usually within five to 10 minutes, blood and gas samples for a second cardiac output determination were collected. Pressure recordings were made immediately before and after the blood sampling.

The subjects were then allowed to breathe room air, the changes in pulmonary arterial pressure again being observed at frequent intervals on the cathode-ray oscilloscope. After it was apparent that the effects of the 13% oxygen breathing had dissipated, usually in 10 to 15 minutes, blood and gas samples for a third cardiac output determination were collected, pressure recordings again being made immediately before and immediately after the samplings.

In addition to the 13 subjects in whom repeated cardiac output determinations were made, pressure changes were recorded before, during, and after breathing 13% oxygen in 15 others. Five subjects breathed 5% CO_2 in air and nine breathed 100% oxygen instead of, or in some instances in addition to, the 13% oxygen in nitrogen, and pressure changes were recorded in a similar fashion.

Mean pulmonary arterial, brachial arterial, and pulmonary "capillary" pressures were determined from the photographic recordings by planimetric integration over two to four respiratory cycles. Pressures recorded through the catheter were corrected for the measured level of the gauges, using 10 cm. above the fluoroscope table as the arbitrary zero point (10). In the cases where the cardiac outputs were determined, the mean pressures immediately before and after collection of blood and gas samples were averaged for use in calculations of resistance.

Pulmonary arteriolar resistance was calculated by the

formula:

$$R = \frac{PA - PC}{CO} \times 1332$$

Where R = arteriolar resistance in dynes sec. cm.$^{-5}$
PA = mean pulmonary artery pressure in mm. Hg
PC = mean pulmonary "capillary" pressure in mm. Hg
CO = cardiac output in cc. per second
1332 = conversion factor from mm. Hg to dynes per cm.^{5}

Total peripheral resistance was calculated according to the formula:

$$TPR = \frac{BA}{CO} \times 1332$$

When TPR = total peripheral resistance in dynes sec. cm.$^{-5}$
BA = mean brachial artery pressure in mm. Hg
CO = cardiac output in cc. per second

RESULTS

(1) *Mean pulmonary artery pressure*

Of 27 subjects who breathed 13% oxygen (see Tables I and II), 20 were normal, four had left ventricular failure due to various causes (Nos. 11, 23, 24, and 25), two had pulmonary emphysema and cor pulmonale (Nos. 27 and 28), and one had early pulmonary fibrosis, cause undetermined. The last patient breathed 13% oxygen during each of two catheterization studies (Nos. 10 and 26).

On 26 occasions, the mean pulmonary artery pressure was satisfactorily calculated before and during 13% oxygen breathing, and was found to rise 0.3 to 14.1 mm. Hg in all but one instance, where it fell 3.3 mm. Hg in a case of cor pulmonale. The average elevation was 24.6% of the control pulmonary artery pressure. In 23 of these subjects the mean pulmonary artery pressure was calculated after recovery from the anoxia, and returned in the direction of the control level or below it in every instance.

The standard error of the mean of the differences (sm) between the mean pulmonary arterial pressures before and during 13% oxygen breathing was determined from standard statistical formulae.[4]

The observed difference of the means divided by sm gave a t value of 6.24. This shows a very significant difference between the two pulmonary arterial pressures, since a t value of 2.79 or above is significant at the 1% level. Thus, the observed differences would occur less often than once in a hundred times by chance alone.

Similar calculations using the differences in pulmonary arterial pressure during and after 13% oxygen breathing showed a t value of 6.75, also indicating a high degree of statistical significance. It is noteworthy that the pulmonary artery pressure before and after recovery from 13% oxygen breathing were not significantly different on statistical analysis.

Because of a possible relationship between hyperventilation and elevation of pulmonary artery pressure, the effect of breathing 5% CO_2 in air—which caused an average increase in ventilation of 280% in a previous series of observations in our laboratory (13)—was recorded in five normal subjects (Table III). As can be seen, there was no consistent change in the pulmonary artery pressures, a slight rise resulting in two instances, and a slight fall in the other three. This finding is in contrast to the 13 cases in Table I where 13% oxygen breathing resulted in less than a doubling of control ventilation minute volume in 11 cases, and slightly more than two times the control value in the other two instances. As has been pointed out, however, marked changes in pulmonary artery pressure occurred in this group. These findings seem to eliminate the mild hyperventilation of 13% oxygen breathing as a contributing factor in the observed elevations of pulmonary artery pressure.

(2) *Mean pulmonary "capillary" pressure*

Satisfactory recordings for determination of pulmonary "capillary" pressure were obtained in 16 subjects before, during, and after the induced anoxia. Twelve of these were normal individuals, three had left ventricular failure and one early pulmonary fibrosis of undetermined cause. (See Tables I and II.)

In 13 of the subjects, no consistent or significant change in the mean pulmonary "capillary" pressure was noted during the entire period of observation. Variations of less than 3 mm. Hg without relation to the inspired gas were observed, and the limits of accepted normal range (10) were not exceeded.

In the three patients with left ventricular failure, changes of greater magnitude were observed,

[4] Fisher, R. A., Statistical Methods for Research Workers. Oliver & Boyd, Edinburgh, 1950, 11th ed., Section 13.

TABLE I

Physiologic effects of breathing 13% O_2

Subject Age. race. sex	Period*	Mean pressures *mm. Hg*			Art. O_2 cont. *vol. %*	Art. O_2 sat. *%*	M.V. O_2 cont. *vol. %*	A-V O_2 diff. *vol. %*	Min. vol. ventilation *cc.*	O_2 cons. *cc./min.*	C. O. *L/min.*	B. S. m^2	Pulm. R. *dynes sec. cm^{-5}*	% Rise pulm. R.
		P. A.	P. C.	B. A.										
1. N. J.	1	14.0	10.1	98.4	14.00	90.8	9.85	4.15	4,283	243	5.52	1.68	56.5	
22 C.M.	2	16.4	11.5	107.1	12.99	84.3	9.03	3.96	7,381	248	6.26		62.6	10.8
Normal	3	15.0	12.6	120.2	14.89	96.6	9.97	4.92	4,756	253	5.14		37.3	
2. N. M.	1	15.8	8.4	62.8	15.02	91.0	11.12	3.90	2,518	160	4.09		144.6	
43 C.F.	2	17.8	8.7	62.3	12.84	77.8	10.18	2.66	3,495	119	4.46	1.60	163.1	12.8
Normal	3	14.0	8.4	72.4	14.97	90.7	11.63	3.34	2,250	143	4.27		104.8	
3. A. H.	1	19.1	6.6		14.45	94.1	10.51	3.94	5,972	271	6.89		145.0	
56 C.F.	2	24.8	7.3		12.08	78.7	7.79	4.29	9,830	219	5.10	1.44	274.2	89.1
Normal	3	18.9	6.5		14.22	92.6	9.12	5.10	5,527	226	4.43		223.7	
4. M. B.	1	18.0	6.7	107.5	18.57	96.1	13.21	5.36	4,270	227	4.24		212.9	
60 C.M.	2	24.5	6.5	105.3	16.15	83.6	11.13	5.02	6,456	201	4.02	1.83	357.9	68.1
Normal	3	18.5	6.1	106.3	18.36	95.0	12.85	5.51	2,743	188	3.41		290.6	
5. P. S.	1	10.4	4.2	97.7	13.98	99.3	10.65	3.33	4,541	198	5.94		83.4	
43 W.M.	2	14.5	4.8	110.6	12.03	85.4	9.16	2.87	9,015	213	7.43	1.60	104.3	25.1
Normal	3	11.2	4.5	110.2	13.21	93.8	10.05	3.16	4,133	208	6.58		81.4	
6. J. R.	1	15.3	4.6		13.10	89.7	9.48	3.62	4,522	203	5.59		152.9	
36 C.M.	2	21.6	4.6		11.12	76.1	7.43	3.69	13,152	224	6.06	1.88	224.2	46.6
Normal	3	15.8	7.0		13.02	89.1	9.06	3.96	5,092	210	5.31		132.4	
7. W. B.	1	14.1	7.5	113.8	14.65	89.7	10.45	4.20	6,320	337	8.02		65.8	
37 W.M.	2	16.8	7.8	105.6	11.79	72.1	7.09	4.70	9,805	306	6.50	1.78	110.6	68.3
Normal	3	13.2	7.6	117.8	14.33	87.7	9.46	4.87	6,211	297	6.10		73.4	
8. C. M.	1	17.2	7.3		15.48	90.3	10.85	4.63	5,185	238	5.13		154.2	
49 W.M.	2	20.9	7.3		13.06	76.2	9.29	3.77	8,526	237	6.30	1.74	172.5	11.9
Normal	3	13.9	6.4		15.15	88.4	11.25	3.90	4,566	209	5.36		111.8	
9. J. S.	1	18.7	7.4		14.87		10.55	4.32	7,055	207	4.78		188.9	
39 C.M.	2	19.0	6.7		13.50		8.77	4.73	7,894	164	3.46	1.85	284.1	50.4
Normal	3	17.2	7.4		14.36		9.02	5.34	5,760	173	3.24		241.7	
10. L. J.	1	26.6	14.4	143.9	16.69	92.7	11.89	4.80	6,056	349	7.27		134.1	
20 C.M.	2	38.3	10.2	126.7	14.09	78.3	10.07	4.02	9,168	334	8.31	2.42	270.2	101.5
Early pul. fib.	3	33.1	11.0	141.7	16.47	91.5	12.52	3.95	7,720	374	9.45		186.9	
11. R. E.	1	43.6		91.5	15.22	93.5	5.39	9.83	4,076	381	1.94			
59 C.M.	2	49.8		103.3	13.10	80.5	3.87	9.23	5,536	317	1.72	1.59		
Congestive failure	3	41.5		78.7	14.39	88.4	5.19	9.20	3,142	354	1.93			
12. C. P.	1				17.80	95.1	13.42	4.38	2,942	236	4.70			
30 C.M.	2				15.38	82.2	11.82	3.56	6,747	225	6.64	1.86		
Normal	3				17.78	95.0	13.57	4.21	4,991	249	6.24			
13. S. S.	1				16.26	94.9	12.49	3.77	3,489	167	4.14			
58 W.M.	2				14.48	84.6	11.70	2.78	8,853	186	6.68	1.96		
Normal	3				15.74	91.9			2,851	165				

P. A. = pulmonary artery pressure
P. C. = pulmonary capillary pressure
B. A. = brachial artery pressure

M. V. = mixed venous
C. O. = cardiac output
B. S. = body surface
R. = pulmonary arteriolar resistance

* Period 1 = control observations
2 = observations during 13% O_2 breathing
3 = observations after recovery

TABLE II

Effect of breathing 13% O_2 in N_2 on brachial artery, pulmonary artery, and pulmonary capillary pressures

Subject Age, race, sex	Diagnosis	Mean press.	Control	13% O_2	Recovery	% Change P. A.
14. C. C. 46 C.M.	Normal	P. A.	16.6	19.5	16.8	+ 17.5
		P. C.	9.9	9.8	12.7	
		B. A.	119.4	115.6	116.8	
15. M. C. 73 W.M.	Normal	P. A.	12.2	13.2	11.9	+ 8.2
		P. C.	11.5	10.7	10.3	
		B. A.	108.0	105.2	106.7	
16. B. A. 21 C.F.	Normal	P. A.	14.0	17.2	15.2	+ 22.9
		P. C.	12.9	9.6	10.4	
		B. A.	103.5	89.7	94.8	
17. W. M. 49 C.M.	Normal	P. A.	17.5	20.2	18.2	+ 15.4
		B. A.	79.9	77.9	72.0	
18. J. M. 22 C.M.	Normal	P. A.	15.9	24.3	22.3	+ 42.1
		B. A.	75.5	80.5	97.9	
19. O. B. 37 C.M.	Normal	P. A.	16.6	30.1	17.9	+ 81.3
		B. A.	98.0	95.0	89.4	
20. H. J. 43 W.M.	Normal	P. A.	16.8	35.9	18.5	+113.7
		B. A.	97.5	107.9	105.6	
21. L. W. 19 W.M.	Normal	P. A.	17.1	22.2	17.1	+ 29.3
22. U. R. 44 C.M.	Normal	P. A.	11.1	13.9		+ 25.2
		B. A.	95.3	100.1		
23. S. J. ? 40 C.M.	Hypertensive C. V. disease cong. fail.	P. A.	26.3	35.3	25.0	+ 34.2
		P. C.	13.6	19.6	13.8	
		B. A.	140.4	144.0	148.3	
24. I. W. 29 C.F.	Post partum myocarditis cong. fail.	P. A.	30.9	39.4	27.7	+ 27.5
		P. C.	24.2	19.1	18.2	
		B. A.	94.5	93.9	93.0	
25. W. B. 54 C.M.	Calcif. pericarditis cong. fail.	P. A.	29.6	37.6	27.6	+ 27.0
		P. C.	11.9	14.7	18.9	
		B. A.	93.0	91.4	92.3	
26. L. J. 19 C.M.	Early pulmonary fibrosis	P. A.	21.1	29.1	23.8	+ 37.9
		B. A.	101.6	75.2	79.8	
27. J. L. 54 W.M.	Emphysema; cor pulmonale	P. A.	35.3	32.0		− 9.3
28. C. C. 40 W.M.	Emphysema; cor pulmonale	P. A.	89.4	93.2		+ 4.2
		B. A.	87.0	96.7		

and the upper limit of normal pulmonary "capillary" pressure was exceeded in each case. One patient showed a progressive rise, another a progressive fall, during the period of observation, and the third showed a transient rise of pulmonary "capillary" pressure during the induced anoxia, with a subsequent fall toward the control value.

No statistical significance could be shown between the differences in pulmonary "capillary" pressure breathing air and 13% oxygen, the t value being 0.22, as compared to the t value of 2.13 required to indicate significance at the 5% level.

(3) *Cardiac output*

In 13 individuals, determinations of cardiac output were made by the direct Fick method before, during, and after the period of 13% oxygen breath-

TABLE III

Effect of breathing 5% CO_2 in air on pulmonary arterial pressure

Subject Age, race, sex	Diagnosis	Mean press.	Control	5% CO_2	Recovery
18. J. M. 22 C.M.	Normal	P. A.	24.6	26.9	19.6
		B. A.	112.3	121.4	101.6
20. H. J. 43 W.M.	Normal	P. A.	17.8	17.3	16.8
		B. A.	95.0	103.1	97.5
21. L. W. 19 W.M.	Normal	P. A.	20.1	18.0	17.8
22. U. R. 44 C.M.	Normal	P. A.	11.9	15.9	11.1
		B. A.	95.8	88.0	97.5
29. H. K. 25 C.M.	Normal	P. A.	21.8	21.2	19.8

ing, as described. Eleven of these subjects were normal, one had left ventricular failure, and one early pulmonary fibrosis by roentgenogram. (See Table I.)

In seven of these subjects who were normal, there was a slight to moderate increase in cardiac output during the period of anoxia, followed by a return in the direction of the control value in the six where the recovery output was determined satisfactorily.

In four of the subjects, a continuous fall in cardiac output was noted during the entire period of observation. This was considered to be due to an elevation of the observed initial value resulting from anxiety, and the finding of a relatively low arteriovenous oxygen difference with a high oxygen consumption at the time of the control determination of cardiac output in three of these individuals (Nos. 3, 7, and 9) confirmed this impression (14). A similar elevation of cardiac output was found during recovery from anoxia in the case of early pulmonary fibrosis (No. 10).

The case with left ventricular failure showed an insignificant diminution of cardiac output during the anoxic period (No. 11).

Statistical analysis of this group as a whole, however, showed the cardiac output during induced anoxia to be not significantly different from that observed during the control or recovery periods.

(4) Pulmonary arteriolar resistance

The pulmonary artery and pulmonary "capillary" pressures and the cardiac output were satisfactorily determined before, during, and after 13% oxygen breathing in 10 individuals, and the respective pulmonary arteriolar resistances were calculated. Nine of these subjects were normal and had normal control values. The patient with early pulmonary fibrosis of undetermined cause had a slightly elevated control mean pulmonary arterial pressure (Table I).

Each subject showed an increase in pulmonary arteriolar resistance during 13% oxygen breathing, with a fall during recovery in the direction of or below the control value. The anoxic increase in resistance varied from 10.8% to 101.5% of the air-breathing level, with an average rise of 48.5%.

Figures 1, 2, and 3 demonstrate the changes in pulmonary arteriolar resistance that were characteristically observed. Figure 1 is taken from the control record of P.S. (case No. 5), at which time the mean pulmonary artery pressure was 10.4 mm. Hg, the mean pulmonary "capillary" pressure was 4.2 mm. Hg, and the cardiac output was 5.94 L/min. The pulmonary arteriolar resistance was 83.4 dynes sec. $cm.^{-5}$.

Figure 2 is taken from the record of the same subject after five minutes of 13% oxygen breathing. At this time the mean pulmonary artery pressure had risen to 14.5 mm. Hg, and the mean pulmonary "capillary" pressure was 4.8 mm. Hg. The cardiac output had risen to 7.43 L/min. and the pulmonary arteriolar resistance to 104.3 dynes sec. $cm.^{-5}$.

Figure 3 represents the same subject 10 minutes after 13% oxygen breathing was discontinued. The mean pulmonary artery pressure had fallen to 11.2 mm. Hg, the pulmonary "capillary" pressure was 4.5 mm. Hg, and the cardiac output was 6.58 L/min. At this time the pulmonary arteriolar resistance had returned to 81.4 dynes sec. $cm.^{-5}$.

The T wave deformity seen in the electrocardiogram (ECG) of the three figures represents an artifact produced by proximity of the left arm electrode to one of the Hathaway variable impedance pressure gauges.

Especially noteworthy was the fact that pulmonary arteriolar resistance increased during anoxia in the four individuals mentioned above in whom the cardiac output fell continuously throughout the observation period. Also the one subject (No. 10) whose cardiac output rose continuously during

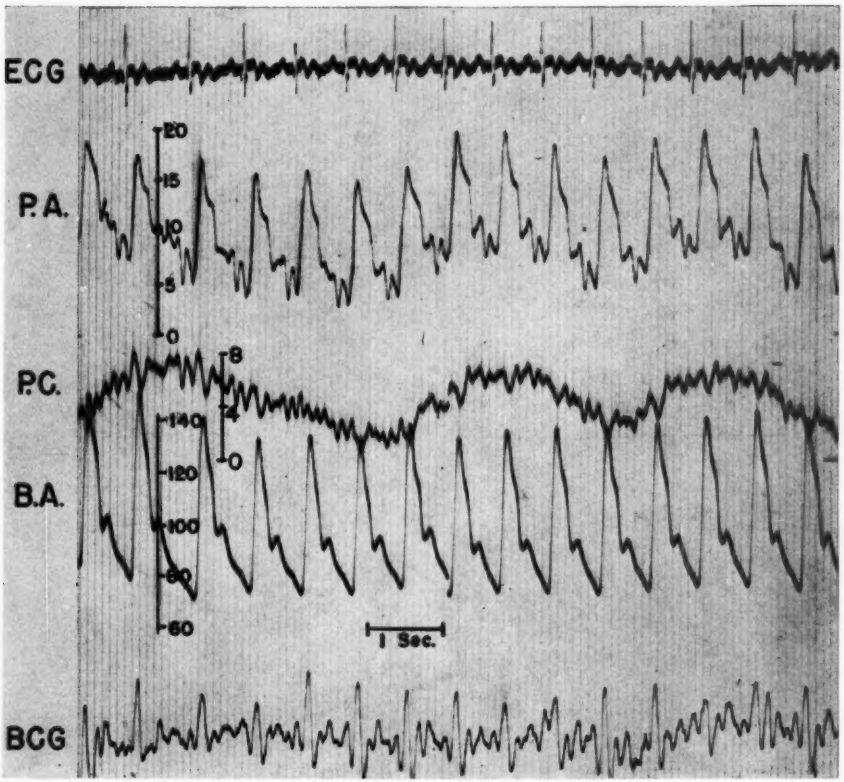

FIG. 1. EXCERPT FROM THE CONTROL PRESSURE TRACING OF P. S. (CASE 5)

The mean pulmonary artery pressure (P.A.) is 10.4 mm. Hg, the mean pulmonary "capillary" pressure (P.C.) is 4.2 mm. Hg, and the cardiac output 5.94 L/min. The pulmonary arteriolar resistance is therefore 83.4 dynes sec. cm.$^{-5}$.

the period of observation, showed a fall in pulmonary arteriolar resistance after discontinuance of the 13% oxygen breathing, as did the other nine subjects. Thus the lack of direct correlation between cardiac output and pulmonary arteriolar resistance was effectively demonstrated in these five cases.

The t value calculated from sm and the observed mean of the differences between the pulmonary arteriolar resistances before and during the induced anoxia, was 3.99. This shows a very significant difference between the two resistances, since a t value of 3.25 or above is significant at the 1% level. Thus, the observed differences would occur less often than once in a hundred times by chance alone.

Similar calculations using the differences in pulmonary arteriolar resistance during and after 13% oxygen breathing showed a t value of 7.44, also indicating a high degree of statistical significance. It is noteworthy that the pulmonary arteriolar resistances before and after 13% oxygen breathing were not significantly different on statistical analysis.[5]

[5] To determine the variability in measurements of mean pulmonary artery pressures and mean pulmonary "capillary" pressures, and in the cardiac output, the following studies were made. In 21 subjects of the present group duplicate resting measurements of pulmonary artery pres-

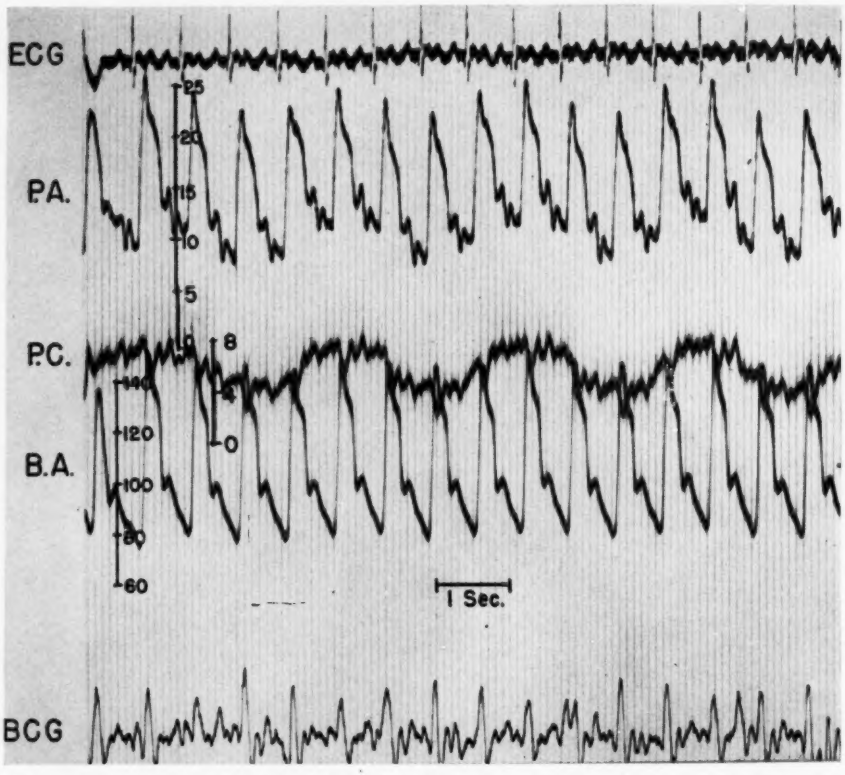

FIG. 2. EXCERPT FROM THE PRESSURE TRACING OF THE SAME INDIVIDUAL AS FIGURE 1, TAKEN AFTER FIVE MINUTES OF 13% OXYGEN BREATHING

The mean pulmonary artery pressure (P.A.) is now 14.5 mm. Hg, the mean pulmonary "capillary" pressure (P.C.) 4.8 mm. Hg, and the cardiac output 7.43 L/min. The pulmonary arteriolar resistance is 104.3 dynes sec. cm.$^{-5}$.

(5) *Related findings*

The brachial artery pressure was measured directly before and during 13% oxygen breathing in 20 subjects, and after the anoxia in 18 of these. No constant variations were noted in the calculated mean pressures, although minor changes of a few mm. Hg in either direction were the rule. The total peripheral vascular resistances before, dur-

sure were made before and after breathing 13% oxygen. In 10 controls duplicate determinations of resting pulmonary artery pressure were made before and after duplicate Fick cardiac outputs. The mean difference between the 31 pairs of measurements in the resting state was 1.7 mm. Hg, giving a standard error of the mean of 1.7 ± 0.58 mm. Hg.

Similar calculations were made for the pulmonary "capillary" pressures, using duplicate resting measurements in the 13 of the present group with normal pressures, and in eight control subjects with normal pressures. The mean difference of duplicate measurements was 1.3 mm. Hg. The standard deviation of the differences was 1.18 mm. Hg. The standard deviation of the mean of the difference was 0.29 mm. Hg, giving a standard error of the mean of the differences equal to 1.3 ± 0.57 mm. Hg.

In nine resting control subjects duplicate determinations of the Fick cardiac output were made. The mean difference in the duplicates was 9.7%. The standard deviation of the differences was 8.14%. The standard deviation of the mean of the difference was 2.9%. The standard error of the mean was 9.7 ± 5.8%.

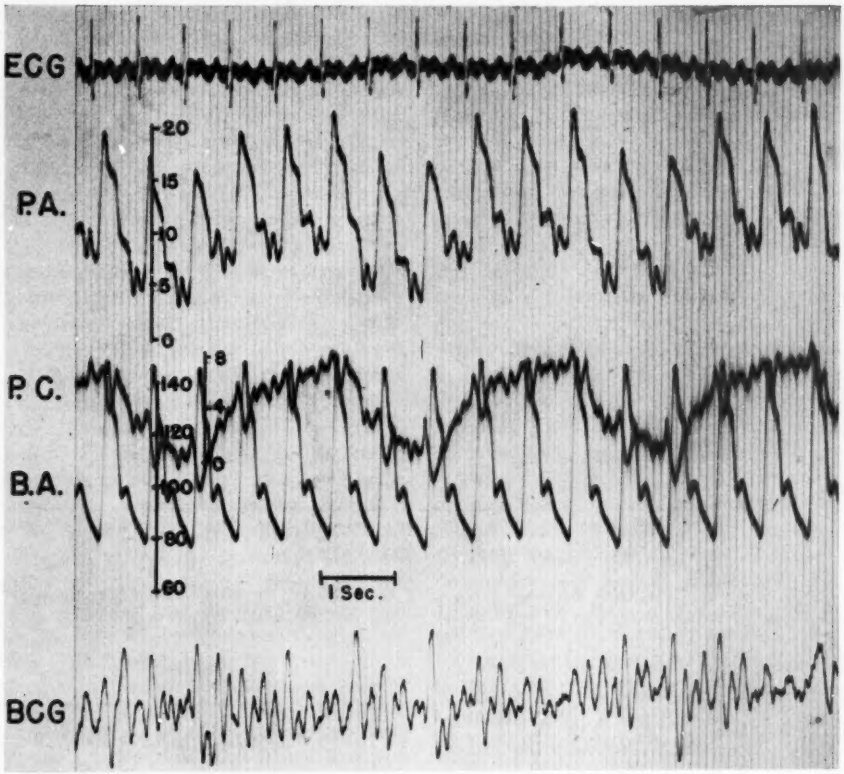

FIG. 3. PRESSURE RECORDING FROM THE SAME INDIVIDUAL AS FIGURES 1 AND 2, TAKEN 10 MINUTES AFTER AIR BREATHING WAS SUBSTITUTED FOR 13% OXYGEN

The mean pulmonary artery pressure (P.A.) has fallen to 11.2 mm. Hg, the mean pulmonary "capillary" pressure (P.C.) is 4.5 mm. Hg, and the cardiac output 6.58 L/min. The pulmonary arteriolar resistance is 81.4 dynes sec. $cm.^{-5}$. Note the change in the ballistocardiogram (BCG) from that in Figure 1.

ing, and after 13% oxygen breathing were calculated in seven of the 13 subjects who had multiple cardiac output determinations. Variations up to 20% of control values were observed in both directions again without constant relation either to the changes in cardiac output or pulmonary arteriolar resistance or to mean brachial artery pressure.

The ballistocardiograms were characterized by relatively normal complexes during control observations on the majority of normal subjects (Figure 1). However, during and after 13% oxygen breathing the complexes invariably became abnormal in such a way that quantitative calculations therefrom were considered to be impossible. An example of the observed change is shown in Figures 2 and 3. It cannot be stated at this time whether these ballistic alterations associated with anoxia were due to a direct effect on the myocardium. A study of this problem and of the relation between cardiac outputs determined from the ballistocardiogram and by the direct Fick method will be considered in a subsequent communication.

In 12 subjects, the arterial oxygen saturation was reduced an average of 13.1% during 13%

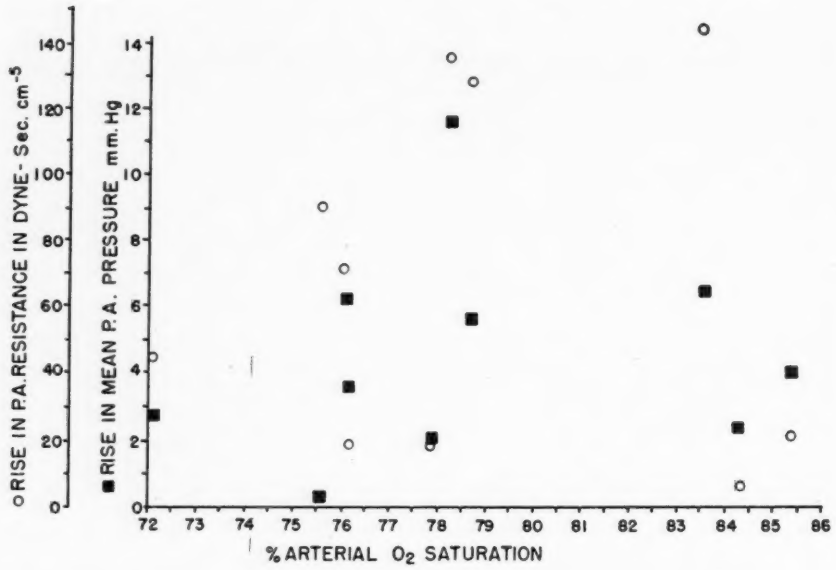

FIG. 4. LACK OF CORRELATION BETWEEN ARTERIAL O_2 SATURATION AND THE OBSERVED ELEVATIONS OF PULMONARY ARTERY PRESSURE OR PULMONARY ARTERIOLAR RESISTANCE

oxygen breathing to levels between 72.1% and 85.4% (av. 79.9% sat.), the mean control saturation being 93.1% (Table I). In the individual cases there was no direct correlation between the specific value to which the arterial oxygen saturation was depressed and the observed elevation of pulmonary artery pressure or pulmonary arteriolar resistance (Figure 4).

The oxygen consumption during 13% oxygen breathing was increased 5 to 21 cc./min. in five of the 13 subjects in whom multiple cardiac output determinations were made and fell 1 to 64 cc./min. in the others, including the patient with left ventricular failure and the four subjects mentioned above whose initial oxygen consumption was considered to be elevated because of anxiety.

During anoxia the arterio-venous oxygen difference fell slightly below the control and recovery values in nine of the subjects in whom this determination was made, and rose slightly in four others, three of whom had the low initial A–V oxygen differences presumably associated with anxiety.

DISCUSSION

Hellems, Haynes and Dexter (8) have presented convincing evidence that the method described by them and employed in the present study for obtaining pulmonary "capillary" pressure in man is valid, and that such pressure is nearly identical and varies directly with pulmonary venous pressure. Pressures obtained through catheters occluding small branches of the pulmonary artery and of the pulmonary vein have been measured by them in dogs (7) and in human subjects having atrial septal defects (8), with the finding of close agreement between the two pressures in each group. Blood obtained from a catheter recording pulmonary "capillary" pressure has been repeatedly found by them (8) and also in our laboratory to be fully saturated with oxygen, indicating the absence of contamination by pulmonary artery blood. Repeated observations by fluoroscopy and by study of continuous pressure tracings during slow withdrawal of the catheter occluding a branch of the pulmonary artery, have shown a slight but definite snap of the tip of the catheter as it suddenly ceases

to obstruct the vessel, and becomes subject to arterial pulsations, which in turn are abruptly recorded on the tracings.

The pressure gradients measured in the present study indicated resistance to the flow of blood from the main pulmonary artery to the capillary bed adjacent to the catheter tip, occluding a small branch of the pulmonary artery. It is assumed that this locally recorded pulmonary "capillary" pressure is representative of the entire lung, and thus can be used in conjunction with the cardiac output to calculate the total pulmonary vascular resistance.

It is apparent from the data presented (particularly of oxygen consumption) that a steady state was not achieved throughout the period of observation in all cases, especially in Nos. 3, 7, 9, and 10, as noted. It is also apparent that the effects of anoxia had not always entirely subsided when the recovery measurements were made. However, the fact that the pulmonary vascular resistances during the anoxic periods always changed in the same direction, and were significantly different statistically from the resistances beforehand and afterward, indicates that the changes observed were independent of variations in oxygen consumption (utilization).

The results indicate that anoxia caused a prompt increase in the pulmonary vascular resistance, which was in turn rapidly dissipated when the anoxia was relieved. This increase in resistance to blood flow must have occurred as a result of vasoconstriction.

Although vasoconstriction in the systemic circulation is largely mediated through the autonomic nervous system, it has been generally believed that the lesser circulation is not subject to autonomic influences. In 1939, Hamilton, Woodbury and Vogt (15) studied the effect of various drugs upon the pulmonary arterial and venous pressures in unanesthetized dogs, and concluded that there was no evidence of autonomic control of the pulmonary circulation. Von Euler and Liljestrand (1), in studying anesthetized cats breathing 10% to 11% oxygen in nitrogen, found that the resulting rise in pulmonary artery pressure was not affected by vagotomy or excision of the stellate ganglia. Since no associated changes in directly measured left atrial pressure were observed (2), the anoxic rise in pulmonary artery pressure was considered to be mediated through a local effect of the degree of oxygenation of the venous blood in the arterioles of the lungs. Dirken and Heemstra (16), however, found that resection of part of the sympathetic trunk increased pulmonary blood flow in rabbits, while vagotomy had no effect. These same observers (17) have reported intense pulmonary constriction in experimental anoxia of the lung exposed to nitrogen while the opposite lung was exposed to oxygen. Previously published data from this laboratory (18) showed that in four of six cases with pulmonary hypertension, intravenous injection of the autonomic blocking agent, tetraethylammonium chloride, caused a significant fall in pulmonary arteriolar resistance. In four patients with normal pulmonary artery pressure, intravenous TEAC did not lower pulmonary arteriolar resistance, suggesting that in some cases of pulmonary hypertension, at least one component of the increased resistance is mediated through the autonomic nervous system.

At the present time, therefore, it has not been determined whether the pulmonary arteriolar vasoconstriction demonstrated to result from oxygen want is mediated through the autonomic nervous system, or depends on a direct local effect upon the pulmonary vessels.

Since the work of Motley and his associates (3) demonstrating the pulmonary hypertensive effect of anoxia in five unanesthetized human subjects, it has been suggested by investigators in the same laboratory (19), McMichael (20) and others, that long-standing pulmonary disease may lead to persistent pulmonary hypertension by the same mechanism which produced it in Motley's acute experiments. The possibility appeared that if one component of chronic pulmonary hypertension is anoxic vasoconstriction, breathing 100% oxygen should reverse this effect, at least in part. Also, it was noted that Von Euler and Liljestrand (1) demonstrated a fall in pulmonary artery pressure of anesthetized cats during 100% oxygen breathing, which they felt might be due to a relief of the excessive desaturation of venous blood inherent in their experimental conditions.

In view of these considerations, the effect on the pulmonary artery pressure of 10–20 minutes of 100% oxygen breathing was recorded in nine subjects (Table IV). Two of these were normal,

TABLE IV

Effect of 100% O_2 breathing on pulmonary arterial pressure

Subject Age, race, sex	Diagnosis	Mean press.	Control	100% O_2	Recovery	% Change P. A.
18. J. M. 22 C.M.	Normal	P. A.	22.3	22.4	24.6	+ 0.4
		B. A.	97.9	101.1	112.3	
22. U. R. 44 C.M.	Normal	P. A.	11.1	12.8	11.1	+15.3
		B. A.	97.5	92.5	95.3	
30. R. S. 68 W.M.	Hypt. C-V disease	P. A.	20.6	21.4		+ 3.9
		B. A.	118.8	128.0		
26. L. J. 19 C.M.	Early pulmonary fibrosis	P. A.	25.4	25.4	21.1	0
		B. A.	100.6	101.6	101.6	
27. J. L. 54 W.M.	Emphysema; cor pulmonale	P. A.	35.1	28.7	35.3	−18.3
28. C. C. 40 W.M.	Emphysema; cor pulmonale	P. A.	88.9	85.3	89.4	− 4.1
		B. A.	98.0	107.7	87.0	
31. G. A. 59 W.M.	Diaphrag. hernia; cor pulmonale	P. A.	41.1	35.3	41.5	−14.1
		P. C.	11.9	15.1	15.6	
		B. A.	104.1	129.0	130.5	
32. D. H. 60 W.M.	Emphysema; cor pulmonale	P. A.	57.4	47.2	47.5	−17.8
33. J. S. 54 W.M.	Emphysema; cor pulmonale	P. A.	39.6	35.3		−10.9

one had compensated systemic hypertension, one early pulmonary fibrosis, and five had chronic pulmonary hypertension with cor pulmonale. A slight rise or no change in mean pulmonary artery pressure was found in the subjects with control values that were normal or nearly so, whereas a definite decline in pulmonary artery pressure was found in the five individuals with chronic pulmonary hypertension. In three of the five, the mean pulmonary artery pressure resumed its previous elevation soon after the subjects were returned to breathing ambient air.

Although no cardiac output determinations were made during these observations, and the number of cases was too small for statistical analysis, the results are consistent with the possibility that anoxic elevation of pulmonary arteriolar resistance may be a contributing and reversible factor in the production and maintenance of at least some types of chronic pulmonary hypertension.

In support of this view is the finding by Cournand (6) of a linear correlation between the degree of arterial oxygen unsaturation and the degree of pulmonary hypertension in a large group of patients with chronic pulmonary emphysema. Factors other than anoxia are usually simultaneously at work, however, as has been clearly pointed out by Ferrer and associates and others (19, 5). Distortion of the pulmonary flow-vascular capacity ratio results in pulmonary hypertension in most types of chronic lung disease when there is increased right ventricular output, hypervolemia, increased blood viscosity due to polycythemia, or progressive anatomic restriction of the pulmonary vascular bed.

Anoxia may also participate in the variety of pulmonary hypertension associated with mitral stenosis and with left ventricular failure. Here the retrograde transmission of rising left atrial pressure is mechanically responsible for a similar rise in pulmonary capillary and pulmonary artery pressure, but with maintenance of an essentially normal gradient in the early stages (9). However, it has been demonstrated by Dexter and his co-workers (10) that when the pulmonary "capillary" pressure in mitral stenosis exceeds a critical value of 20–25 mm. Hg an additional element of pulmonary arteriolar constriction supervenes, resulting in a further precipitous rise in pulmonary artery pressure. Since this critical range of pul-

monary "capillary" hydrostatic pressure approximates the osmotic pressure of plasma (21), it appears reasonable to assume that the delivery of oxygen from the alveolar air to the pulmonary capillary blood may be interfered with due to excessive congestion and beginning edema formation. The role in this embarrassment played by thickening of the capillary basement membrane in mitral stenosis (22) remains a matter of conjecture. However, the arteriolar constriction which provides the abrupt increment in pulmonary artery pressure observed in both mitral stenosis and in left ventricular failure (10, 23) may in turn be the result of anoxia.

Dexter and his associates (10) have pointed out that this increased resistance may be considered teleologically as a compensatory mechanism preventing to some extent sudden increases in flow through the capillaries to the incompetent left ventricle or to the narrow mitral valve and therefore protecting the pulmonary capillaries from a higher hydrostatic pressure and pulmonary edema. It appears likely that such a mechanism may be initiated by anoxia.

Although anoxia and its attendant increase in pulmonary arteriolar resistance may be regarded as a common denominator in many instances of pulmonary hypertension, it should be emphasized, as pointed out by Liljestrand (2), that the same mechanism may also provide valuable local regulation of blood flow normally, and in conditions where there is unequal oxygenation in various parts of the lung. The flow of blood will be directed away from parts of the lung which are badly aerated and distributed to parts where the purposes of the lesser circulation can be better fulfilled, without noticeable change in the pulmonary artery pressure.

It has been pointed out by Cournand (6) that such delicate adjustment is notably absent in chronic pulmonary disease, where, in addition to pulmonary hypertension, one of the principal causes of physiologic disorder is the disturbance in local alveolar ventilation-perfusion relationships.

SUMMARY

1. The effects of anoxia on the human pulmonary circulation were studied by means of cardiac catheterization.

2. On 26 occasions, 13% oxygen breathing caused an average rise in mean pulmonary artery pressure of 24.6% above the control levels.

3. No significant change in mean pulmonary "capillary" pressure was observed in 16 subjects who breathed 13% oxygen.

4. No statistically significant change in cardiac output could be attributed to anoxia in 13 subjects in whom multiple Fick determinations were made.

5. Simultaneous determinations of mean pulmonary artery and pulmonary "capillary" pressures and cardiac output were made before, during, and after 13% oxygen breathing in ten individuals. The pulmonary arteriolar resistances calculated therefrom showed an average increase of 48.5% during the low-oxygen breathing, a difference which is shown to be highly significant statistically.

6. Changes observed in the systemic blood pressure, total peripheral resistance, ballistocardiogram, arterial oxygen saturation, oxygen consumption, and arterio-venous oxygen difference are described.

7. Evidence for and against autonomic mediation of the observed anoxic pulmonary vasoconstriction is reviewed.

8. The increase in pulmonary vascular resistance observed to result from anoxia is discussed as to its probable contribution to the pulmonary hypertension of chronic lung disease, mitral stenosis, and left ventricular failure.

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THE MOTION OF THE THORAX DURING THE HEART CYCLE: A COMPARISON OF LONGITUDINAL, LATERAL AND DORSO-VENTRAL BALLISTOCARDIOGRAMS[1]

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The lateral motion of the body during the cardiac cycle has been observed by Yandel Henderson and others who recorded the motion of a table on which the subject reclined (1). Antero-posterior, lateral and longitudinal recording (2), and recording of lateral motion at three levels simultaneously with the longitudinal ballistocardiogram (3) also has been carried out with the table method but in each case only a few records have been reproduced. When motion was recorded from three points along the side of a table, the foot moved in the opposite direction from the head and shoulders (3). It is therefore to be expected that records of lateral motion of the entire body will have less amplitude than records of motion at the level of the chest.[2]

With the introduction of photoelectric and electromagnetic methods (4) for recording the longitudinal ballistocardiogram directly from the body it was logical to attempt recordings of lateral thoracic motion by these methods for the purpose of determining possible "typical patterns" for the various congenital cardiac anomalies associated with right to left or left to right shunts. The lateral motion of the body may be recorded from any desired point, but we consider motion at the thoracic level of the greatest interest, and the level of the xiphoid process in the right midaxillary line the most useful and reproducible. Recordings from a similar position on the left may be interfered with by the apex thrust when the heart is large.

Using multichannel apparatus we have recorded the right lateral ballistocardiogram simultaneously with the electrocardiogram and longitudinal ballistocardiogram in 50 subjects without valvular disease, in 20 subjects with various congenital cardiac anomalies, and in a few subjects with acquired valvular disease. The electromagnetic pick-up, filtered to reduce somatic tremor, gives waves coinciding in time with those recorded simultaneously by the photoelectric method of the Starr table.

Lateral or dorsoventral records can be made with electromagnetic pick-ups with a hinged arm on which the coil moves in relation to a fixed magnet, or the magnet on a hinge moves in relation to a fixed coil. Contact can be made directly, with the hinge touching the body and swinging in the chosen plane. We have found the best contact is made by mounting a ball-point so as to project from the hinge in the line of motion and by fixing a glass slide over the surface of the skin at the chosen point. This gives a frictionless contact when the surface of the slide is parallel to the sagittal and longitudinal axis of the body and prevents picking up motion in any but the lateral direction; when parallel to the horizontal plane and longitudinal axis, only dorsoventral motion is recorded. (See Figure 1; A, B and C.)

The direct recording ballistocardiogram can be standardized in terms of either velocity or bodily motion. By applying tension to the body, and releasing the tension, the relation of displacement to applied force can be quantitated for each patient just as can be done for various table methods. On the average, the displacement of the body in a longitudinal ballistocardiograph on the direct method gives a 1 cm. deflection or 1 mv. of current, when a pull of 125 to 150 grams applied by cords over the shoulders is released. In the lateral plane, standardization is less simple. In general when the longitudinal and lateral records are recorded simultaneously lateral waves are recorded at 2–4 mm./mv. and longitudinal at 1 cm./mv. At these settings the largest waves have about the same amplitude. A similar ratio exists between dorsoventral and longitudinal recordings. Since no need for quantitation arose in our work, this matter has not been pursued. We are interested in relative size and timing of waves, not in the absolute force represented by a

[1] Supported by a grant from Federal Security Agency, Public Health Service, National Institutes of Health, Bethesda, Maryland.

[2] Scarborough and associates (2) suggest the use of antero-posterior ballistocardiograms, in concordance with radiologic practice, rather than use of dorsoventral, as used by Hamilton, Dow and Remington (1), or by Braunstein, Oelker and Gowdy (3). There are two disadvantages—lack of precision, since antero-posterior axes of quadrupeds and bipeds are at right angles, and three extra syllables. We adhere to the original and the more precise and concise terminology. In all tracings in this report, headward, rightward and ventral motion are upward deflections.

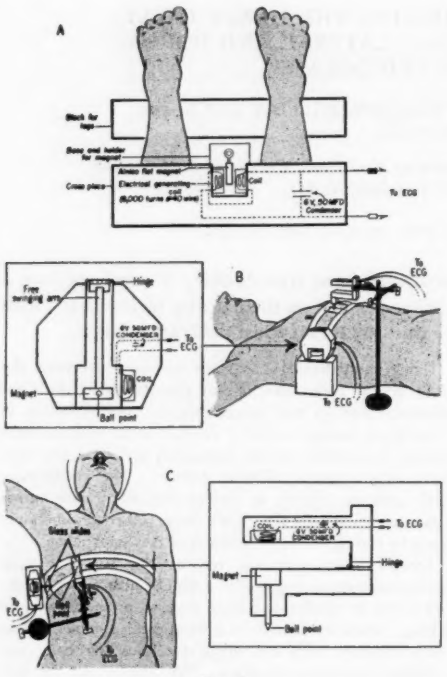

FIG. 1

A. Positioning of ballistocardiograph across shins for recording the longitudinal ballistocardiogram. A block is placed under the Achilles tendon to raise the thighs off the table to minimize damping by friction. *B* and *C*. Positioning of ballistocardiographs for recording the lateral and dorsoventral ballistocardiogram. A fourth channel (not shown) records the electrocardiogram simultaneously.

given wave. All longitudinal traces were recorded at 1 cm./mv., laterals and dorsoventral traces at a sensitivity which gave easily read curves. This rarely was more than 4 or less than 2 mm./mv.

The fact that thoracic motion caused voltage changes two to five times as great as longitudinal motion of the entire body does not mean that the forces in the lateral and dorsoventral directions are greater than those in the longitudinal plane. The force actually reaches the skeleton through the mediastinum, and motion of the thorax in the lateral and dorsoventral directions is great because the thoracic cage can respond to mediastinal tugging without equally great motion of the entire skeleton in the lateral and dorsoventral directions, but not in the longitudinal direction, where the skeleton is far more rigid. With a table, which records the total force acting on the entire body, lateral and dorsoventral motion will be far less than in direct thoracic records.

As seen in Figure 2, tracings from the optimal point (right midaxillary line at the level of the xiphoid) show larger and more regular waves with fewer small oscillations than those taken 10 cm. cephalad or caudad. The direction and timing of all the main waves in these positions are similar. The point giving greatest amplitude will vary from subject to subject depending upon body build, or even in the same subject with respiration suspended in different phases of respiration. As is evident in Figures 3 and 5, the position of the rib cage and diaphragm has far more effect on the lateral than on the longitudinal ballistocardiogram. The effect is chiefly on the amplitude of the waves,

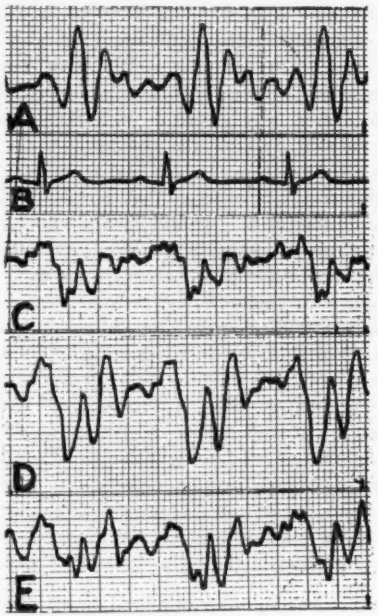

FIG. 2

A. Longitudinal ballistocardiogram. *B*. Simultaneous electrocardiogram. *C*. Right lateral ballistocardiogram recorded 10 cm. cephalad to the level of the xiphoid. *D*. Right lateral ballistocardiogram at the level of the xiphoid. *E*. Right lateral ballistocardiogram 10 cm. caudad to the xiphoid. All records were made from the most lateral point on the thorax which was about in the midaxillary line. In these traces rightward motion coincides with the headward H and J, leftward with the footward I and K. Lateral traces lined up by their coinciding electrocardiograms.

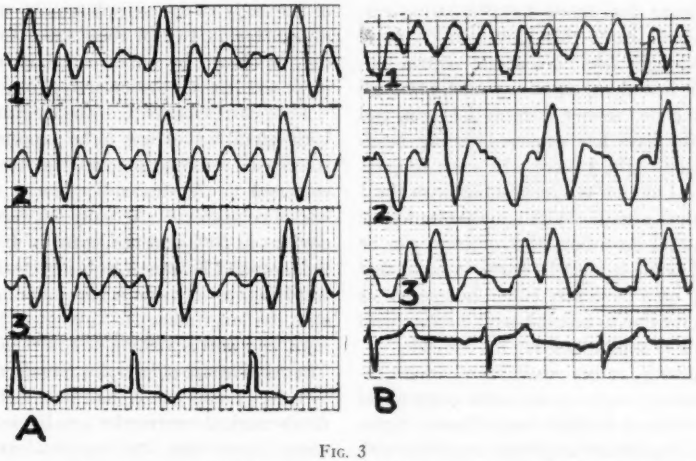

FIG. 3

Group *A* are longitudinal tracings. Group *B* right lateral traces. Tracings *A1* and *B1* taken in deep inspiration; *A2* and *B2* tracings during mid-position of respiration; *A3* and *B3* tracings during deep expiration. Lower tracings of *A* and *B* are the electrocardiograms fitting the tracings. The respective longitudinal and lateral tracings were taken simultaneously. Marked changes in the lateral traces occur with only slight changes in the longitudinal. Usually the I–J amplitude is larger in held inspiration than in expiration. In this experiment with deep inspiration there was sufficient Valsalva effect to cause a relative decrease in I–J amplitude.

not on their direction or on the time relation of peaks and troughs to those recorded in the longitudinal plane.

Curves obtained by high frequency tables moving laterally may show leftward motion synchronous with the headward H and J waves (2, 3), although Hamilton and associates present, as a characteristic curve, rightward and dorsal motion synchronous with the J wave (1). The latter relationship is what one would predict from the rightward and dorsal path of the jet of blood in the aorta, and this is the relationship usually seen in direct records of lateral motion of the thorax. It seemed possible that torsion of the thorax might occur, and in flat-chested people this might result in apparent leftward motion of the lateral convexity even though the thorax as a whole was moving to the right. If the torsion rolled the supine body to the right, the table would be pushed to the left, thus explaining the relative frequency of leftward motion of the table synchronous with the headward J waves.

We attempted to investigate the possibility of torsion by making records of vertical motion in the right and left mid-clavicular lines at the level of the xiphoid. Even on a hard surfaced table (Fig-

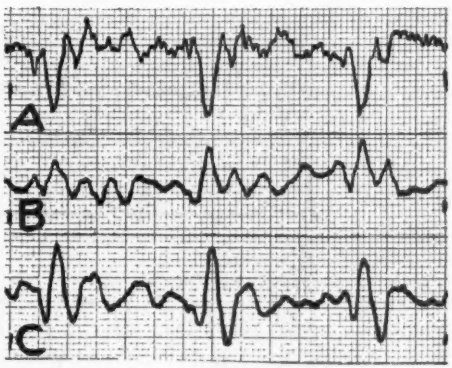

FIG. 4

A. Vertical motion of the thorax in the right midclavicular line at the level of the xiphoid. *B*. Simultaneous right lateral tracing. *C*. Simultaneous longitudinal tracing. Note sharp posterior motion simultaneous with rightward and headward J wave. The left vertical shows slight ventral motion at this time, but is distorted by the apex thrust which precedes it.

ure 4), the thorax does move dorsally during systole, and in most cases this movement is more marked on the right side. No actual ventral motion of the left hemithorax was recorded, although dorsal motion ended sooner than on the right, and a return to the base line occurred during headward inscription of the J wave. In some subjects the right dorsal motion is synchronous with the I wave rather than with J. With simultaneous table and direct lateral recording, this problem can be solved. Meanwhile it must be borne in mind that torsion acting on a table may either exaggerate or reverse the force due to actual lateral displacement when the body is supine or lying on one side.

Not infrequently, rather small lateral waves coincide with major systolic waves in the longitudinal tracing. In subjects without heart disease, rightward waves of significant amplitude coincided with the headward H wave in 57% of our tracings, but in 12% there was a leftward wave of comparable amplitude. Synchronous with the footward I wave in the longitudinal ballistocardiogram was a significant leftward wave in 45% and a rightward wave of comparable amplitude in 8% of the lateral records; rightward waves with the headward J wave appeared in 30% of the tracings and a corresponding leftward wave in 12%. Whether the motion opposite to that expected is due to torsion of the body or true displacement was not determined, but in two of these cases torsion did occur, as shown by dorsoventral records from the right and left midclavicular regions.

Poor correspondence of the longitudinal K wave with lateral waves was to be expected, since K is inscribed by forces generated as the blood is decelerated in the descending aorta, with minimal lateral component. Actually leftward motion was obvious in 10% and rightward in 4%, at the time the footward K wave was being inscribed. Rightward waves of significant amplitude coincided with the longitudinal L wave in 25% of the tracings, and corresponding leftward waves in 16%. The relative size of lateral waves decreased from H to I, I to J, and J to K, and then increased with L. As the auriculoventricular axis lies in a more transverse plane than the ventriculoarterial, lateral forces incident to systolic ejection might be relatively small, and those associated with venous pulse waves or with rapid ventricular filling relatively large. The latter would cause the large diastolic displacements of the lateral ballistocardiogram. Not infrequently a straight line in the lateral ballistocardiogram occupied the time covered by large waves in the longitudinal ballistocardiogram (Figure 5E). While the diastolic waves in the longitudinal ballistocardiogram rarely exceed the

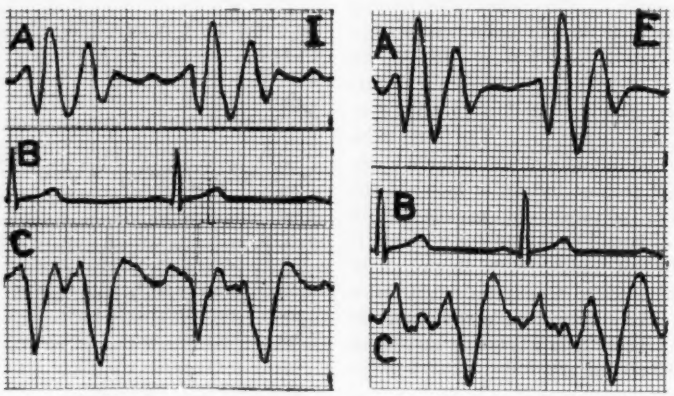

FIG. 5

In Figures 5–10: *A*. Longitudinal ballistocardiogram. *B*. Electrocardiogram. *C*. Right lateral ballistocardiogram.

Here, the left group of traces were taken in deep held inspiration, and the right group in deep held expiration. The diastolic waves are larger than systolic in the lateral trace, and much more altered by respiratory phase.

systolic waves in amplitude, this is quite often noted in the lateral records (Figure 3 [mid-position], Figure 5E).

It is tempting to relate waves in the ballistocardiogram with the motion of the heart, and especially with the apex impulse at the onset of systole. Experimental studies account for all the waves of the I–J–K complex without any apex impulse (5) and the H wave often is tall in cases of heart disease in which an apex beat is not palpable. In the lateral ballistocardiogram there is seen, in rare instances, a sharp rightward motion synchronous with the H wave and possibly due to recoil from the apex thrust. Sudden leftward motion is also occasionally recorded at the same point in systole in other subjects (Figure 6). No such abrupt motions are ever noted in other parts of the cycle, or in longitudinal traces. The subjects who exhibit such abrupt motion do not have unusually forceful apex beats; in some no thrust is palpable.

Of interest are the tracings from a patient with multiple valvular lesions and an enormous heart which fills almost the entire chest cavity. This patient exhibits an extremely forceful apex beat. Her longitudinal tracing reveals slurred and notched J wave and a very deep M wave, with a total of three marked upward and downward waves

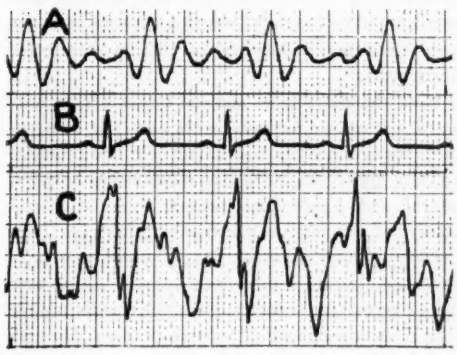

FIG. 6

Note the sharp leftward motion (downward on the trace) synchronous with the H wave. Such abrupt motion is only found in lateral traces, is rarely rightward, and while it occurs with isometric contraction there is no apparent relation of such a motion to a violent apex thrust. In this subject the apex thrust was not visible and was barely palpable.

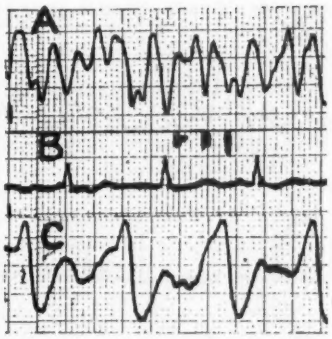

FIG. 7

From a patient with a violent apex thrust and a huge heart, due to rheumatic valvular disease. Dots on the electrocardiogram show approximate times of first, second and very loud third heart sounds. Comment in text.

in each cycle. The lateral ballistocardiograms (Figure 7) show only one wave per cycle with no significant motion synchronous with the apex beat or the J wave. There is slow rightward motion in late systole, accelerated rightward motion synchronous with L and a steep and deep leftward wave synchronous with the footward M wave and with a loud protodiastolic gallop. Her longitudinal ballistocardiogram recorded from the shin electromagnetically in 1951 is identical with that recorded from the head with a pulse recorder in 1948 (see Figure 1 in reference 6).

The longitudinal ballistocardiogram of a patient with complete heart block showed no waves related to auricular beats, and the I–J–K–L complexes varied only slightly with P–R intervals ranging from 0.16 to 0.80 seconds. The lateral traces were much the same with P–R intervals of 0.16 to 0.30 seconds, but quite different with intervals of 0.52 and 0.64 seconds (Figure 8). Auricular beats coinciding with the phase of early diastolic filling greatly augmented early diastolic rightward motion (L wave), which was much larger than any of the other waves, while auricular beats 0.16 to 0.30 seconds before the R wave produced a leftward displacement which was sustained throughout the entire I–J–K complex. Auricular waves in mid-diastole produced a rightward and then a leftward displacement.

Of special interest were the tracings on one elderly man with myxedema (Figure 9), and of

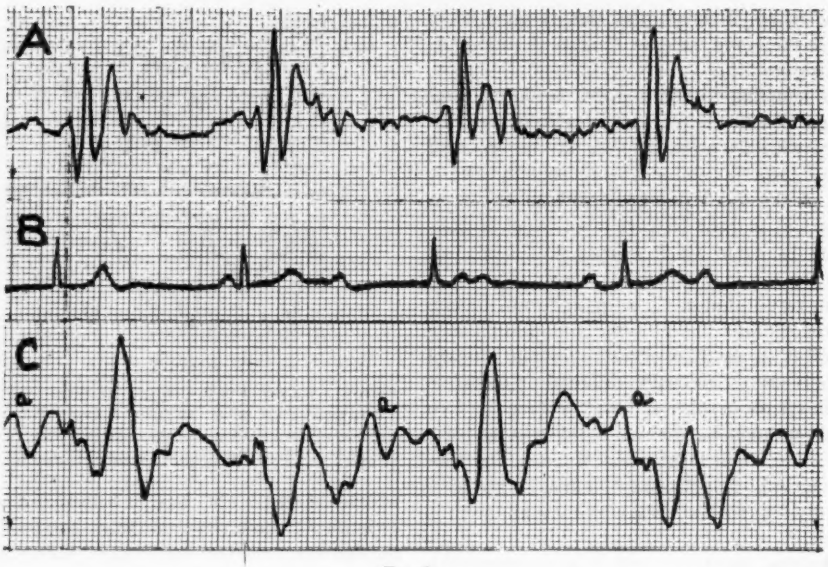

FIG. 8

From a case of complete heart block; a, in lateral trace, marks auricular complexes in mid-diastole. Comment in text.

another with angina pectoris following myocardial infarction (Figure 10). Both had featureless small waves in the longitudinal tracings, and very definite large waves in the laterals. One reason for this may be in the difference in natural vibration of the body in the longitudinal and lateral directions. While the frequency is about the same, damping of after waves is much greater in the lateral when the left chest wall is tapped, than in the longitudinal when the shoulder is tapped. It is, therefore, difficult to set the body in oscillation with repeated small impulses laterally, but this appears to occur not infrequently in longitudinal motion with feeble heart beats.

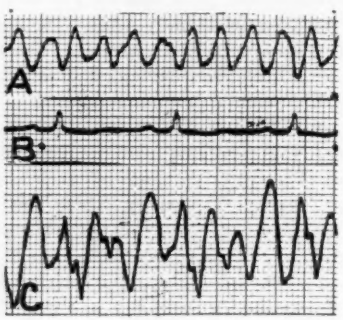

FIG. 9

From a case of myxedema. Continuous, characterless waves in the longitudinal trace, with distinct pattern of different phase in the lateral.

Both the above cases showed rather abrupt leftward motion synchronous with isometric contraction, though neither had a palpable apex thrust. In both there was no phase relationship between lateral and longitudinal waves and the lateral traces had one less peak and trough per cycle than the longitudinal records. Diastolic motion greatly exceeded systolic in the lateral curves. In no case did we record in the lateral plane the chaotic jumble seen in some longitudinal records of cases of angina or infarction, but in few of our cases were records made without suspending respiration, which usually diminishes the irregularity of the waves in such cases.

Most of the young congenital cardiacs we studied had longitudinal and lateral records which showed no remarkable features as compared with

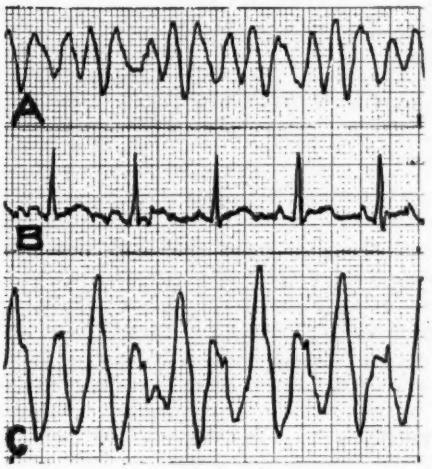

FIG. 10

From a case of angina pectoris. The J–K excursion, the largest in a longitudinal trace composed of simple oscillations, coincides with the peak of a rightward wave which begins with the trough of I and ends with the peak of L.

controls. Indeed, there is no consistent relation of lateral thoracic ballistocardiographic patterns even to marked right or left axis deviation; the waves were the reverse of the common pattern in one case of situs inversus. More careful studies on a larger number of cases verified by catheter technics may reveal correlations between lateral thoracic ballistocardiograms and such shunts or acquired valvular lesions. The simplicity of recording the lateral motion whenever precordial leads are being inscribed with four-channel recorders makes it seem desirable to do so in many cases of suspected myocardial disease as well as in valvular disease. Perhaps the most significant fact apparent in these tracings is that return flow and cardiac filling in diastole produce lateral motion of the thorax comparable to the longitudinal motion of the body caused by ventricular systole.

CONCLUSIONS

With electromagnetic pick-ups and a multichannel recorder the dorsoventral lateral motions of the thorax and the longitudinal motion of the body can be inscribed simultaneously with the electrocardiogram.

The lateral motion varies in amplitude at various levels in the right midaxillary line; the level of the xiphoid was chosen for systematic study.

Lateral motion is altered more than longitudinal by the phase of respiration in which the tracing is inscribed or by variations in the P–R intervals in a given subject.

In many normal subjects lateral motion during diastole is much greater than during systole, presumably because blood moves from right to left as the ventricles are filled. In general rightward and headward, leftward and footward motions are recorded with direct thoracic tracings. This conforms with the fundamentals of ballistic theory when the rightward and headward direction of the cardiac axis is considered.

Dorsoventral motion recorded from the right and left midclavicular lines seems to indicate torsion of the trunk in systole. This may explain the leftward and headward systolic motion recorded by table ballistocardiography, for such torsion would push the table in a direction opposite to the roll of the body.

No relation of congenital or acquired lesions to characteristic lateral ballistocardiograms was detected.

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FOREWORD

The six papers which follow present the results of extensive studies of the effects of administration of carboxylic cation exchange resins as reflected in electrolyte and nitrogen balances under a variety of circumstances.

The complete data proved to be so extensive as to present a real problem because of the excessive printing costs involved, and publication was made possible by a grant from the National Drug Co. to defray the cost of reproducing the many tables and figures.

THE EDITORS

AN INTRODUCTION TO EXPERIMENTAL AND CLINICAL STUDIES OF CARBOXYLIC CATION EXCHANGE RESINS

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Problems in the regulation of the composition and volume of body fluids in health and in disease states fall into three general groups which involve either *a*) maintenance of the *status quo,* assuming it is not far removed from normal, or *b*) replacement of depleted body stores of water, electrolytes, or colloids, or *c*) removal of constituents present in excess. Judicious prescription or interdiction of extracellular and cellular ions and water, based on a knowledge of external and internal exchanges, will often suffice in the first two categories (1–8). On the other hand even marked restriction of intake may not lower, for example, body sodium or potassium in the third group. In these instances limitation of intake will be effective only if negative external balances of sufficient magnitude are achieved by losses of these ions in urine, sweat, gastrointestinal secretions, or stools (9–13). In many clinical situations this can be accomplished with relative ease. Thus edema of varied etiology can be controlled or actually cleared through sodium and water diuresis during salt restriction (14–17). In other instances of congestive failure, cirrhosis, or renal disease with or without significant hypoalbuminemia this regimen proves ineffective, even when sodium ingestion has been reduced essentially to zero and even though simultaneous diuretic measures may be employed (18–20). Similarly in renal disease, as in anuria, the kidney can no longer jettison excesses of ions such as potassium, sodium, or chloride (21–23).

Under such circumstances only a limited number of therapeutic procedures have been available prior to the introduction of cation exchange resins, all relatively complicated. The various dialyzers which can be used to remove electrolytes from blood require complex apparatus and constant attention (24–28). Also untoward reactions related either to cellophane or to inadequacies of the dialyzing fluid are not uncommon. The latter limitation is likewise present in the alternatives of intestinal or peritoneal lavage together with the additional disadvantage of relative inefficiency and, in the second of these two, the risk of uncontrollable infection (12, 29–32). Finally, the growing body of evidence that sodium restriction may be beneficial in certain vascular diseases (33) will extend to a wider segment of the population the burden of the unpalatability of the truly salt-free diet.

Preliminary studies with cation exchange resins indicate that these substances offer a new approach to the control and correction of excessive retention of cations in body fluids (13, 34–37). They can interfere with the absorption of sodium, potassium, and probably calcium and magnesium from the gastrointestinal tract. Furthermore, they may also remove endogenous stores of some of these ions since under ordinary physiological circumstances relatively huge amounts of these body electrolytes are secreted into the gastrointestinal tract and subsequently reabsorbed (3). Once attached to the resin they may be excreted via stools, producing desired, or at times undesirable, negative balances. In the latter instance the problem is simple since, as indicated earlier, replacement of body constituents is possible.

One additional point should be made in view of the findings to be presented in subsequent papers of this study: the removal of positive ions by resins must inevitably be accompanied by a release of some other cation in equivalent amounts. It is obvious that if these particles are in turn absorbed they may of themselves produce distinct effects. The experimental findings to be presented in this series of studies substantiate this.

An understanding of the properties of the synthetic cation exchange resins in general and of the carboxylic type in particular will help in the interpretation and explanation of many of the biochemical effects which we have noted in our ex-

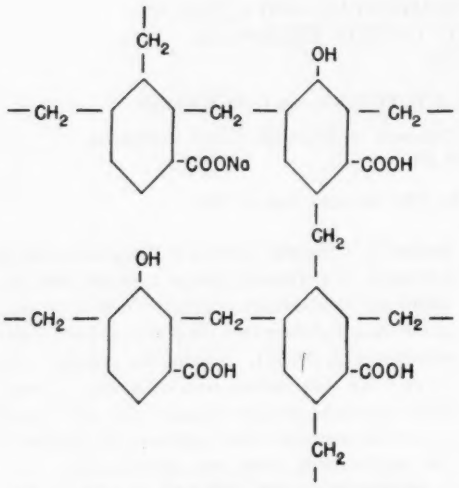

FIG. 1. CHEMICAL FORMULA OF A SYNTHETIC CARBOXYLIC CATION EXCHANGER

A schematic representation of a segment of a carboxylic cation exchange resin in the hydrogen form or cycle. One of its hydrogen ions has been replaced by sodium after exposure to a sodium chloride solution. Exchanger $-COOH + NaCl \rightleftarrows$ Exchanger-COONA $+ HCL$. The CH_2 groups unite the benzene rings of the polymer in chains and cross linkages which limit the swelling of the resin in aqueous or organic solvents. The degree of this swelling is governed by their frequency in the molecular unit.

perimental subjects. These agents are polymers of aromatic hydrocarbons such as phenolsulfonic acid or benzoic acid linked and cross linked by short, stable, and virtually indestructible carbon chains contributed by the condensing agent, usually formaldehyde (38–40) (Fig. 1). Chemical groups available for the cation exchange process, such as the sulfonic ($-SO_3H$), carboxylic ($-COOH$), or phenolic ($-OH$), are attached to the benzene ring. In aqueous and other solutions these resins take in water or the particular organic solvent in which they may be suspended and increase in bulk. In this state they can properly be spoken of as gels. The swelling is attributable to the fact that the hydrogen ion or any other cation associated with the acid radical ionizes and exerts an osmotic pressure. The exchange resin when wet therefore has many of the properties of an acid or of a concentrated salt solution. In the transformation from the dry to the wet state water or other solvents penetrate the surface and enter the interstices of the resin structure until the osmotic pressure of the fluid inside the resin particle, together with the resistance exerted by the linkages and cross linkages, exactly equals the osmotic pressure on the outside (41, 42). Insofar as the distribution of electrolytes is concerned, equilibria are attained which are quite in keeping with the Gibbs-Donnan effect, at least in the more concentrated solutions. Hence anions common to both the gel and the circumambient solution will always be present in lower concentration in the resin, whereas the reverse will be true of the associated cations. It is obvious therefore that the exchange processes cannot be explained by simple adsorption.

The property which permits the exchange of one cation attached to a resin for another in its environment is fundamentally based upon the fact that resins have different degrees of affinity for the different cations. Thus the same exchanger under the same physical conditions exposed to a dilute solution containing identical concentrations of magnesium, calcium, and sodium will preferentially bind larger amounts of magnesium than of calcium, and more calcium than sodium. The characteristics of the cations themselves which are known to show a positive correlation with the affinity of the exchanger for a particular cation include valence, atomic weight, and the radius of the unhydrated ion. These orders of preference recur irrespective of the attending anions, with the proviso that they not be of the type which form complex salts (38–42). The hierarchy of affinities evident in dilute solutions is readily upset, however, by increases in the concentration of one of the competing cations, by alterations in the pH of the solution, by replacement of water with other solvents, and, finally, by increased swelling of the resin (43).

The carboxylic cation exchangers employed in our studies in general share with the sulfonic and phenolic resins all of the above-described features. In their acid properties, however, the carboxylic resins differ from the other two types of resin, occupying an intermediate position. Thus with pH values greater than 3.5, replacement of the carboxylic group hydrogen by other cations occurs to a progressively greater extent and ultimately reaches a maximum. The sulfonic resins on the

other hand are strongly acidic and can function maximally at any pH value; the phenolic exchangers are weakly acidic, ionize only to a slight degree and remain relatively inert until pH values high in the alkaline range are attained. It is obvious that of these three groups of agents the pH range over which the carboxylic resin functions as an exchanger and its relatively weak acidic properties which can be readily buffered in body fluids render it most suitable for biological administration. Further theoretical advantages of the carboxylic resins over the sulfonic acid derivatives include the fact that the latter have a lower exchange capacity and that they may produce abrupt changes in local and systemic acid-base balances (38–44).

As the lower pH ranges are approached the greater affinity of the carboxylic cation exchangers for the hydrogen ion becomes more and more manifest and other cations are progressively displaced until at pH values of 3.5 or less the exchanger reverts entirely to the hydrogen form. It is probable that irrespective of the form or cycle in which the resin is given, it is converted in the stomach to the hydrogen form. Therefore, the net effect of giving the sodium derivative of the resin is that of administering a cation with an unabsorbable anion.

The studies to be presented reveal a relatively low *in vivo* capacity of this particular resin for sodium and potassium compared to those demonstrable at similar pH values *in vitro*. This should not be surprising since it is obvious that other cations, particularly calcium, magnesium, iron, and organic cations, can preferentially assume positions in the resin. Furthermore, interference of organic substances such as lipids, steroids, and proteins with the exchange process has not been defined.

The arrangement and sequence of this and of the papers which follow arose from a combination of necessity and predetermined plan. The studies in animals using large per kilogram dosage preceded the administration of these agents to human subjects. The second paper, therefore, describes serum, urine, stool and balance findings during the administration to dogs of a carboxylic cation exchanger in one of two cycles or forms (45). Human studies in which resins were ingested in a variety of cycles make up the third paper (46). In these investigations sodium usually was not markedly restricted; control stool data were obtained from a large group of subjects maintained on either whole milk, a diabetic diet, a regular diet or a so-called "salt-free" regular diet. These data are presented in the tables and figures of the papers which follow; when necessary, they have been supplemented by acceptable control material. In the fourth paper, attributes of the individual cycles of the resin evident in the preceding paper have been measured during the simultaneous administration of two or more of the polymers in varying proportions, and employed in attempts to cancel certain toxic effects of ACTH and cortisone (47). The results have been evaluated against the control background described in the preceding paper. The possible influences of the steroids and of the trophic hormone or hormones of the adrenal on stool composition have been defined elsewhere (48). The fifth unit reports the events which occur in nephrotic children to whom an acidifying exchanger is administered during the course of essentially complete sodium restriction (49). In the sixth and final paper attempts are made to summarize and interconnect the findings of all the studies, to list logical sequellar investigations, and to predict the probable clinical utilities of the resins (50).

A word about the cooperative character of these studies is in order. Examination of the tabulated material in the papers which follow will reveal that the bulk of the work embodied in this collection is based on a substantial number of balance periods in dogs and in patients. These data were gathered in a period of 16 months, and their collection and completion would have been quite impossible without the active and time-consuming cooperation of many others besides the individuals appearing as co-authors. The people and organizations who have generously given time, effort, and frequently funds to support this investigation are listed in the following section. A special mention should be made, however, of the contribution of the patients themselves who not only cooperated, but often participated actively in assisting us to assure complete and accurate collections.

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CARBOXYLIC CATION EXCHANGE RESIN EFFECTS IN DOGS

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Reports describing trials of exchange resins in removing cations from the gastrointestinal tract of experimental animals have been limited to toxicity studies and to measurements of the relative magnitudes of the oral intake and the stool output (1–3). In the experiments presented in this paper changes in serum, urine, and stool components, as well as the external and internal balances of certain electrolytes and of nitrogen have been determined in dogs receiving a carboxylic cation exchange resin in one of two forms. The chemical and physical characteristics of these agents have been described in detail in the introductory paper (4).

MATERIALS AND METHODS

Mongrel female dogs, maintained on a commercial feed ("Friskies") [1] and allowed free access to water, received a carboxylic cation exchange resin in the hydrogen or the sodium form for periods of seven to 11 days. In some instances beef extract or milk and sugar were used to enhance palatability, but many animals nonetheless lost weight partly or entirely as a consequence of anorexia induced by the regimens employed. Since this occurred to an equal degree when control and recovery periods of comparable length were alternated with resin periods it represented a common denominator in our experiments. The beginning and the end in each interval of the study were marked by catheterization of the urinary bladder, measurement of body weight and withdrawal of venous blood for analysis of blood nonprotein nitrogen (NPN) and sugar, and of serum carbon dioxide content, chloride, sodium, potassium, calcium, phosphorus and water, using previously described methods (5–7). The pH of anaerobic samples of serum was determined by means of the glass electrode. Food and resin intake, stool and urine output as well as any vomitus or rejected food were collected, measured, and analyzed separately for nitrogen, sodium, potassium and chloride content (8–10). Stools were removed from the cage and weighed immediately. Procedures for partitioning the external balances into extracellular and cellular components have been described only in part in previous publications (11–17) and are therefore appended in detailed form.

[1] Content per 100 g.: Na, 17.6 meq.; K, 10.2 meq.; Cl, 16.2 meq.; and N, 3.42 g.

With but minor exceptions all findings have been subjected to conventional statistical analyses (18). In the case of the body weight and the serum constituents values observed at the end of each control, experimental, or recovery interval were subtracted from those present at the start of the particular period under scrutiny and expressed as increments or decrements ($\pm \triangle$). After the means of these changes had been calculated (values greater than 2 S. D. were discarded) the resin and post resin values were compared with those of the control periods. Changes were considered significantly different statistically when "p" for the "t" test was 0.05 or less. Urinary and stool output and the balance data were analyzed in terms of *per diem* values. The constituents of the stools have in addition been expressed in relation to stool mass as well as in terms of stool nitrogen. The data are presented in three tables; the statistical evaluation has been summarized in Table IV and in Figures 1 through 3.

RESULTS

I. Experiments with the carboxylic cation exchanger in the hydrogen cycle

A. Serum constituents: Table I and Figure 1 reveal that the administration of the hydrogen cycle resin produced a decrease in the serum sodium, carbon dioxide content or bicarbonate, and water concentrations, while the levels of chloride increased. The decrement of water was too small in magnitude, however, to account for the change in chloride. In some instances the change in carbon dioxide was accompanied by a fall in pH. All of these alterations disappeared following withdrawal of the resin. The mean decrease in serum potassium during resin therapy and the subsequent changes during recovery were not significant.

B. Losses in stool: Ingestion of the cation exchanger in the hydrogen cycle was accompanied by increases in the excretion of sodium and potassium in feces without alteration in the losses of chloride and nitrogen (Table II and Figure 2). These observations, together with the failure to demonstrate any statistically significant increase in stool weight during resin ingestion even though

TABLE I

Body weight and analyses of blood and serum in dogs receiving an exchange resin in the H or the Na cycle

Subject	Time	Therapy		Body Wgt.	Blood		Serum							
(Age-Sex)	(days)	H (g./d.)	Na	(kg.)	Sugar (mgm%)	NPN (mgm%)	HCO$_3$ (meq./l.)	Cl (meq./l.)	Na (meq./l.)	K (meq./l.)	Ca (mgm%)	P (mgm%)	H$_2$O (g./l.)	Protein (g.%)
236A	0	0	0	8.20	80	41	-	113.2	140	4.9	-	6.9	935	5.95
	0-1	0	0	-	-	45	21.4	108.0	156	4.6	11.9	7.0	936	
	1-7	0	0	8.55	72	41	21.8	111.9	157	4.9	11.1	8.8	943	
	7-14	0	0	8.70	70	37	22.2	108.4	-	5.8	-	7.1	941	
	14-21	34	0	9.23	77	42	14.0	121.3	154	4.8	8.8	7.6	947	
236A[1]	0	0	0	9.30	70	38	23.8	106.5	158	5.6	-	6.4	901	
	0-6	0	0	10.10	-	36	19.1	111.0	156	4.1	10.3	6.6	938	
	6-13	40	0	9.60	-	29	16.0	117.5	160	5.6	-	6.8	-	
	13-20	0	0	9.68	64	32	20.9	114.7	160	4.5	9.0	6.2	936	
	20-27	0	40	10.38	74	32	21.1	108.8	157	4.5	9.4	7.2	938	
243B	0	0	0	9.48	85	32	21.6	108.8	145	5.2	-	5.2	920	7.03
	0-1	0	0	-	-	-	22.2	103.3	158	4.6	11.9	3.8	925	
	1-7	0	0	9.68	81	29	21.5	109.4	156	4.7	10.5	5.6	923	
	7-14	40	0	7.95	86	79	14.0	93.2	-	4.3	-	3.9	889	
	14-21	0	0	9.18	88	31	23.4	111.3	-	4.7	8.6	4.6	917	
243B[1]	0	0	0	9.60	64	32	20.4	109.2	156	5.8	-	4.5	931	
	0-6	0	0	10.00	-	32	16.7	107.0	-	4.2	11.0	4.8	915	
	6-13	34	0	9.48	-	25	11.8	113.7	-	4.5	-	3.8	-	
	13-20	0	0	10.18	66	33	22.9	111.3	156	4.8	-	4.9	925	
	20-27	0	40	10.62	72	30	24.5	108.3	156	5.7	11.0	5.2	929	
246C	0	0	0	6.00	94	35	17.0	116.8	154	4.7	-	4.2	933	6.74
	0-1	0	0	-	66	34	20.8	113.5	164	3.9	11.2	4.4	936	
	1-7	0	0	6.00	79	28	21.2	112.4	159	4.6	11.4	3.7	-	
	7-14	0	0	5.60	68	29	22.7	113.2	-	5.4	-	4.6	934	
	14-21	0	0	5.63	76	35	19.7	114.5	152	4.9	12.2	4.4	919	
247D	0	0	0	8.82	73	32	20.0	112.4	143	4.9	-	5.1	943	4.35
	0-1	0	0	-	61	29	22.4	108.7	157	4.6	10.3	5.0	-	
	1-7	0	0	8.98	68	31	23.4	113.5	156	4.8	10.1	4.8	-	
	7-14	40	0	9.15	65	33	17.4	118.0	-	4.7	-	4.4	945	
	14-21	0	0	9.53	67	30	22.9	112.6	156	4.9	9.8	4.0	932	
247D[1]	0	0	0	9.15	-	29	21.8	113.0	145	4.3	-	4.3	917	
	0-6	0	0	9.80	-	30	22.3	110.5	161	4.7	9.7	4.2	936	
	6-13	40	0	9.30	-	29	-	119.2	157	-	10.9	3.7	942	
	13-20	0	0	9.38	61	32	23.7	112.8	159	4.7	9.5	3.8	936	
	20-27	0	40	10.00	72	31	25.0	107.2	156	5.0	8.3	4.0	940	
188E	0	0	0	17.55	-	46	21.7	113.3	142	5.4	-	5.0	951	
	0-5	0	0	17.58	-	34	20.1	111.6	161	4.8	10.1	4.8	937	
	5-12	40	0	17.73	-	27	20.2	113.0	156	4.5	11.6	4.0	942	
	12-19	0	0	18.03	75	32	20.7	112.6	156	5.0	11.6	3.7	938	
	19-26	0	40	18.28	79	34	22.4	110.8	160	4.6	11.1	4.8	940	
190	0	0	0	10.66	-	32	22.4	113.6	152	4.3	10.3	1.7	937	
	0-10	0	0	10.33	-	27	22.9	111.4	155	4.6	10.2	2.2	933	
	10-15	0	0	9.54	-	26	18.4	111.0	148	3.9	-	-	937	
246	0	0	0	6.10	-	33	19.5	113.8	149	4.7	11.2	2.3	930	
	0-10	0	0	5.84	-	30	19.5	117.3	162	4.7	11.4	2.6	-	
	10-15	0	0	5.41	-	34	22.4	102.2	133	4.0	-	-	932	
75515	0	0	0	19.02	-	32	19.9	111.4	156	4.2	11.0	1.5	931	
	0-10	0	0	18.74	-	27	20.9	110.6	160	4.3	10.8	1.8	923	
	10-15	0	0	18.12	-	27	18.4	104.7	138	3.9	-	-	935	
92516	0	0	0	15.24	-	25	22.9	110.3	150	4.1	10.7	1.7	932	
	0-10	0	0	15.01	-	31	22.5	108.9	146	4.5	10.5	2.2	927	
	10-18	60	0	14.29	-	35	13.8	115.6	143	4.2	-	-	-	
382	0	0	0	11.85	-	34	20.6	110.5	145	4.7	-	-	924	
	0-11	41	0	11.25	-	25	19.4	115.6	149	4.3	9.5	2.5	936	
	11-20	0	0	11.02	-	31	21.4	114.4	141	4.8	-	-	928	
	20-30	0	30	10.73	-	26	22.3	101.1	154	4.5	10.0	2.7	932	
	30-41	0	0	10.32	-	27	22.6	109.4	148	4.4	10.3	3.4	932	
	41-48	0	0	10.24	-	29	19.4	112.3	148	4.8	11.6	-	-	
391	0	0	0	9.93	-	29	20.1	112.3	150	4.4	-	-	934	
	0-11	33	0	8.20	-	31	9.7	117.4	148	3.9	9.2	5.4	951	
	11-20	0	0	8.53	-	31	20.3	114.6	153	4.8	-	-	944	
	20-30	0	30	8.26	-	28	23.0	112.9	152	4.2	9.7	2.4	941	
	30-41	0	0	7.88	-	32	20.6	113.5	143	4.6	9.8	3.0	940	
	41-48	0	0	7.66	-	30	20.1	113.4	153	4.3	9.9	2.6	942	
404	0	0	0	9.65	-	25	21.6	105.7	140	4.3	-	-	942	
	0-11	35	0	8.50	-	29	17.0	117.5	152	4.1	10.2	-	933	
	11-20	0	0	8.25	-	28	23.4	97.0	141	5.4	-	-	946	
	20-30	0	30	8.09	-	28	22.7	112.1	155	4.4	11.0	1.4	944	
	30-41	0	0	7.80	-	30	20.3	112.9	143	4.3	11.5	-	-	
	41-48	0	0	7.62	-	30	25.3	108.6	153	3.9	11.2	6.0	-	

the mean values did increase, indicate that the changes described above were not related to increased stool mass. Following withdrawal of the resin, the excretion of sodium and potassium returned to levels characteristic of the control periods.

C. Losses in urine: The average daily urine volumes rose during hydrogen cycle resin treatment without loss of body weight (Table II), pointing to increased exchanges of water. From the data available it is not possible to decide whether this change in urine volume was a manifestation or a cause of a greater intake of water. Concomitantly it was noted that the mean levels of sodium and of potassium in urine decreased on resin therapy, together with a diminution in the total daily excretion of these electrolytes (Figure 2). The first of these changes can be ascribed, at least in part, to the increased urine volumes, but the second suggests a diminished excretion of sodium and potassium in urine reciprocal to the increased losses of these electrolytes in stools described earlier. This possibility is supported by the observation that the resin did not alter the output of chloride and nitrogen in stools and that the urinary chloride and

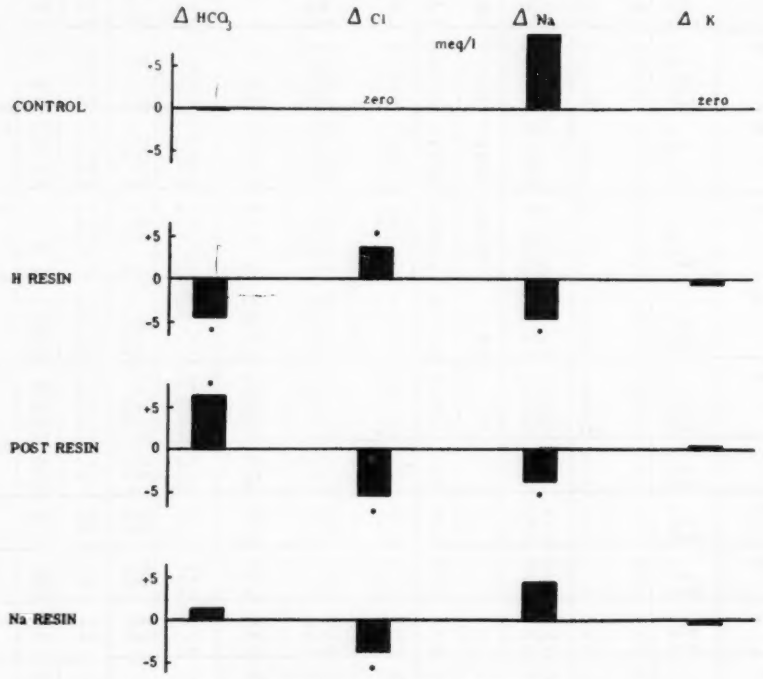

FIG. 1. ALTERATIONS IN SERUM CONSTITUENTS

Mean changes in serum constituents between the onset and the end of the indicated experimental periods are depicted in terms of milli-equivalents per liter. Asterisks identify statistically significant differences ("p" values of 0.05 or less) upon comparison with the changes in the control periods. The statistical summary (Table IV) contains the actual values employed in setting up Figures 1, 2, and 3 of this paper. During H resin ingestion the serum bicarbonate decreased with a subsequent return to control levels during the post resin period. Similarly, the hyperchloremia present at the end of H resin therapy disappeared in the recovery interval. Relative hyponatremia which appeared in the H resin period persisted into the post resin interval. The sodium form of the exchanger lowered serum chloride. Serum potassium remained relatively constant throughout all studies. Though not presented above, the same was true of serum calcium, phosphorus and protein while the mean serum water increased by 0.006 g./l.

TABLE II

Intake data and urine and stool output in dogs receiving an exchange resin in the H or the Na cycle

Subj.	Time	Therapy		Intake					Urine					Stool				
		H	Na	Fluid	Cl	Na	K	N	Vol.	Cl	Na	K	TN	Wgt.	Cl	Na	K	N
	(days)	(g./d.)		(l.)	(meq.)	(meq.)	(meq.)	(gm.)	(l.)	(meq.)	(meq.)	(meq.)	(gm.)	(gm.)	(meq.)	(meq.)	(meq.)	(gm.)
236A	0-7	0	0	ad lib.	316	343	199	66.7	0.90	293	317	163	41.5	1335	45	80	35	23.2
	7-14	0	0		389	423	245	82.1	0.98	351	372	211	46.6	1760	43	89	41	27.7
	14-21	34	0		716	481	585	90.9	2.94	659	315	575	54.4	2415	42	275	71	45.3
	0-6	0	0		292	317	184	61.6	0.86	279	78	109	41.1	1464	32	145	34	24.8
	6-13	40	0		393	437	282	82.3	1.91	287	193	197	41.9	2347	42	246	73	34.2
	13-20	0	0		340	370	214	71.8	0.89	316	294	186	45.6	1542	51	145	41	30.7
	20-27	0	40		395	1449	284	82.3	1.89	348	942	222	46.5	2165	33	493	78	35.4
243B	0-7	0	0	ad lib.	310	337	195	65.5	1.06	254	210	181	46.7	2063	72	200	40	21.3
	7-14	40	0		163	95	148	17.4	2.38	98	16	38	34.0	897	40	158	102	9.9
	14-21	0	0		316	343	199	66.7	4.68	200	168	111	44.8	1351	13	76	39	12.0
	0-6	0	0		292	317	184	61.6	1.57	254	214	156	39.2	1378	34	145	28	8.3
	6-13	34	0		207	234	160	43.0	3.82	195	57	132	35.9	1085	15	216	106	15.6
	13-20	0	0		340	370	214	71.8	1.92	310	270	155	50.3	1397	37	142	30	21.6
	20-27	0	40		241	1288	187	49.8	2.05	215	656	149	35.3	1221	22	553	44	14.8
246C	0-7	0	0	ad lib.	111	121	70	23.4	0.32	70	65	47	12.6	610	25	56	13	8.8
	7-14	0	0		323	132	278	25.7	0.44	237	81	193	14.3	527	33	50	17	8.0
	14-21	0	0		170	185	107	35.9	0.40	116	92	92	19.3	953	40	92	20	13.0
247D	0-7	0	0	ad lib.	316	343	199	66.7	0.93	296	245	180	36.4	1660	39	184	38	27.8
	7-14	40	0		345	421	234	76.4	1.30	283	34	114	48.0	2314	50	437	155	37.1
	14-21	0	0		557	377	448	77.0	1.50	513	220	420	43.2	2018	49	177	54	32.9
	0-6	0	0		292	317	184	61.6	0.88	254	266	161	39.1	1603	20	101	26	-
	6-13	40	0		385	430	272	80.6	1.24	335	99	230	36.7	2441	22	363	89	33.0
	13-20	0	0		340	370	214	71.8	0.85	320	258	180	48.3	1721	32	143	34	26.0
	20-27	0	40		394	1454	282	82.0	1.68	311	907	234	45.9	2235	32	584	67	34.3
188E	0-5	0	0	ad lib.	292	317	184	61.6	1.52	242	281	185	42.5	1031	24	87	22	20.3
	5-12	40	0		385	430	272	80.6	2.80	347	196	242	52.1	1862	49	320	64	32.2
	12-19	0	0		340	370	214	71.8	1.32	258	241	161	39.3	1146	36	126	30	25.1
	19-26	0	40		394	1454	282	82.0	2.39	325	818	257	46.8	1723	57	607	65	32.1
190	0-10	0	0	ad lib	162	176	102	34.2	1.50	190	215	181	47.3	427	6	38	8	8.9
	10-15	0	0		0	0	0	0	0.69	50	19	31	14.6	103	3	51	12	1.0
246	0-10	0	0	ad lib.	162	176	102	34.2	0.59	123	118	106	27.8	776	32	95	30	12.3
	10-15	0	0		0	0	0	0	0.77	48	23	28	12.2	120	6	49	34	2.4
75515	0-10	0	0	ad lib.	162	176	102	34.2	1.54	179	188	159	42.4	382	17	23	4	7.3
	10-15	0	0		4	5	1	2.7	2.00	67	15	31	16.0	292	8	54	44	2.7
92516	0-10	0	0	ad lib	173	254	164	113.2	2.26	118	187	190	89.9	837	11	57	22	10.3
	10-18	60	0		111	189	112	85.7	2.71	91	21	76	65.6	1114	15	238	119	15.7
382	0-11	41	0	ad lib.	301	355	145	36.0	2.36	261	104	88	41.1	694	10	226	107	3.6
	11-20	0	0		412	501	143	41.9	3.00	408	470	160	39.9	461	12	62	18	-
	20-30	0	30		458	1667	159	46.5	2.58	355	882	145	38.4	1238	6	527	57	15.0
	30-41	0	0		504	613	175	51.1	2.94	480	540	244	57.9	565	9	62	15	9.6
	41-48	0	0		321	390	111	32.5	1.80	305	364	154	33.8	489	10	31	22	6.2
391	0-11	33	0	ad lib.	115	204	60	25.5	1.99	72	18	61	30.4	334	12	128	65	4.0
	11-20	0	0		412	501	143	41.9	1.98	412	384	142	36.8	837	29	104	30	14.7
	20-30	0	30		458	1667	159	46.5	2.62	460	1077	154	41.3	1215	30	674	67	14.4
	30-41	0	0		504	613	175	51.1	2.11	456	528	215	47.3	734	15	49	15	10.1
	41-48	0	0		321	390	111	32.5	1.49	289	307	-	34.9	378	13	27	18	7.0
404	0-11	35	0	ad lib.	200	213	95	30.0	2.30	156	62	59	29.7	464	30	163	96	5.7
	11-20	0	0		412	501	143	41.9	1.53	428	674	158	36.5	497	20	81	38	7.0
	20-30	0	30		458	1667	159	46.5	2.94	415	989	159	37.9	1162	38	605	64	15.4
	30-41	0	0		504	613	175	51.1	2.22	435	459	232	42.9	565	17	65	17	7.7
	41-48	0	0		321	390	111	32.5	1.38	242	258	142	27.9	237	8	22	20	3.1

nitrogen merely decreased in concentration but not in the total amount lost per unit of time. In the periods following resin the volume and composition of urine returned to values indistinguishable from controls.

D. Balance data: Subtraction of the electrolytes and nitrogen lost in stools, urine and occasionally in vomitus from the respective intake of these constituents in food revealed that during the administration of the hydrogen cycle resin the losses of potassium from the body were increased without any statistically significant change in the balances of chloride, sodium or nitrogen (Table III and Figure 3). The negative values characteristic of

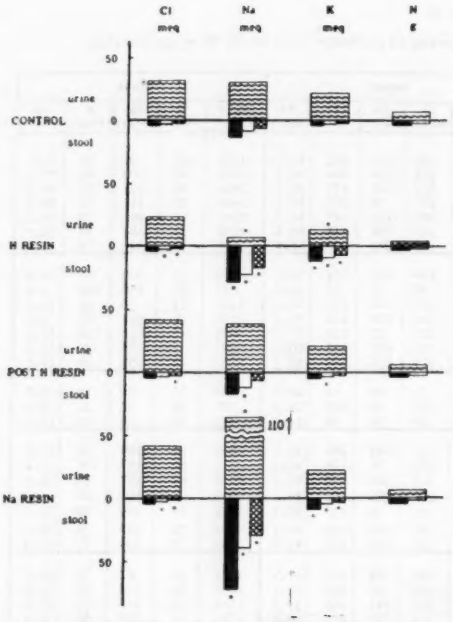

FIG. 2. DAILY EXCRETIONS OF ELECTROLYTES AND OF NITROGEN IN URINE AND IN STOOLS—PRESENTED AS MEAN VALUES

Columns with horizontal waves depict daily urinary excretion of the constituent. The smaller columns below the horizontal lines are based on stool data. Black columns refer to per day values, open columns indicate excretion per 100 g. of stool and the crosshatching identifies the electrolyte : nitrogen ratio. The small circles indicate that the change in the mean from the control is statistically significant.

Ingestion of the H form of the resin increased the stool excretion of potassium and of sodium above control values. This was accompanied by decreased urinary output of these electrolytes. The sodium form of the resin also raised the stool potassium and sodium. Urinary potassium in these experiments, however, did not decrease below control values; urinary sodium on the other hand rose markedly. The changes in stool chloride were present only irregularly and were of small magnitude, and no significant alterations occurred in urine chloride. Nitrogen excretion was not altered.

the control periods reflect the anorexia and weight loss cited earlier.

Partitioning of the balances into extracellular and cellular phases reveals that the observed negative values for potassium represent losses of this electrolyte from cells. Further, corrections for the anabolism or catabolism of protein indicate that these negative balances represent losses of cell potassium with, as well as in excess of, nitrogen. The mean change in extracellular sodium was of insufficient magnitude to result in an increased negative external balance. They do indicate, however, that under the aforementioned experimental conditions, the hydrogen form resin can remove sodium from the chloride space as well as lower the serum sodium levels.

II. Experiments with the carboxylic cation exchanger in the sodium cycle

A. Serum constituents: In contrast to the hydrogen form of the resin, the exchanger charged with sodium did not produce acidosis, hyperchloremia nor hyponatremia (Table I and Figure 1). A mean decrement of − 3.6 meq./l. did occur in the serum chloride concentration.

B. Losses in stool: The effects of the sodium cycle resin on stool constituents were qualitatively similar to those observed during hydrogen resin therapy (Figure 2). As might be expected from the greater intake of sodium in using the exchanger in the sodium cycle, this cation appeared in much greater amounts in the stool. At the same time there occurred an approximately two-fold increase in the amount of potassium excreted each day in contrast to the three-fold rise observed in the hydrogen resin studies. Stool mass, stool chloride and stool nitrogen did not vary significantly from the control values.

C. Losses in urine: Ingestion of the carboxylic cation exchanger in the sodium cycle was associated with increases in urine volume (Table II) and decreases in urine potassium and nitrogen concentration quite comparable to those recorded in the hydrogen resin experiments (Figure 2). On the other hand, in contrast to the results in the first group of studies, the animals receiving the sodium cycle resin showed an increase in the daily urinary sodium output. These reflected of course absorption and subsequent urinary excretion of sodium released from the sodium form of the resin. Finally, it should be pointed out that the doubled output of potassium via the gastrointestinal tract was not accompanied by a compensatory fall in the uri-

TABLE III

External, extracellular, and cell balances in dogs receiving an exchange resin in the H or the Na cycle

Subject	Time	Therapy		Ext. Bal.				Extracell. Bal.			Cell Bal.			
(Dog)	(Days)	H (g./d.)	Na	Cl (meq.)	Na (meq.)	K (meq.)	H (gm.)	H_2O (l.)	Na (meq.)	K (meq.)	H (gm.)	Na (meq.)	K (meq.)	K** (meq.)
236A	0-7	0	0	- 25	- 59	+ 1	+ 1.7	-0.2	- 1	-1	+ 1.7	- 58	+ 2	- 2
	7-14	0	0	- 7	- 41	- 7	+ 7.6	0	- 3	+1	+ 7.8	- 38	- 8	-27
	14-21	34	0	+ 13	-112	-61	- 9.0	0	- 11	-2	- 9.3	-101	-59	-37
	0-6	0	0	- 21	+ 91	+41	- 4.5	0	- 43	-4	- 4.4	+134	+45	+55
	6-13	40	0	+ 62	- 5	+12	+ 6.0	+0.4	+ 68	+5	+ 6.4	- 73	+ 7	- 8
	13-20	0	0	- 29	- 72	-13	- 4.7	-0.2	- 28	-3	- 4.9	- 44	-10	+ 2
	20-27	0	40	+ 12	+ 11	-16	+ 0.2	+0.2	+ 27	+1	+ 0.2	- 16	-17	-17
243B	0-7	0	0	- 19	- 78	-26	- 2.8	-0.2	- 6	-2	- 2.6	- 72	-24	-18
	7-14#	40	0	- 65	-108	-35	-34.1	-0.4	- 49	-2	-34.1	- 59	-33	+48
	14-21	0	0	+101	+ 96	+49	+ 9.7	+0.6	+ 90	+3	+ 9.7	+ 6	+46	+23
	0-6	0	0	+ 2	- 45	0	+13.9	0	+ 9	-3	+13.9	- 54	+ 3	-30
	6-13#	34	0	- 18	- 46	-81	-10.0	-0.2	- 40	0	- 9.6	- 6	-81	-58
	13-20	0	0	- 9	- 45	+29	- 0.3	0	- 5	0	- 0.8	- 40	+29	+31
	20-27	0	40	+ 2	+ 76	- 6	- 0.5	+0.1	+ 10	+2	- 0.3	+ 66	- 8	- 7
246C	0-7	0	0	+ 13	- 5	+10	+ 1.7	+0.2	+ 30	0	+ 1.4	- 35	+10	+ 7
	7-14#	0	0	- 7	- 21	+29	- 1.5	-0.1	- 16	+1	- 1.5	- 5	+28	+32
	14-21	0	0	+ 12	- 1	- 5	+ 3.4	+0.1	+ 8	0	+ 3.2	- 9	- 5	-13
247D	0-7	0	0	- 22	- 91	-19	+ 2.2	-0.2	- 8	-1	+ 2.2	- 83	-18	-23
	7-14	40	0	+ 10	- 53	-35	- 8.9	0	+ 3	0	- 9.0	- 56	-35	-14
	14-21	0	0	- 7	- 23	-26	+ 0.7	0	+ 4	0	+ 0.9	- 27	-26	-28
	0-6	0	0	+ 16	- 53	- 3	-	+0.2	+ 59	+2	-	-112	- 5	-
	6-13	40	0	+ 26	- 35	-47	+10.7	+0.1	- 1	0	+10.8	- 34	-47	-73
	13-20	0	0	- 14	- 34	0	- 2.7	0	+ 5	0	- 2.9	- 39	0	+ 7
	20-27	0	40	+ 49	- 40	-19	+ 1.6	+0.5	+ 76	+3	+ 1.7	-116	-22	-26
188E	0-5	0	0	+ 22	- 56	-23	- 1.6	+0.2	+104	-1	- 0.2	-160	-22	-22
	5-12	40	0	- 13	- 89	-34	- 3.9	-0.1	- 43	-2	- 3.1	- 46	-32	-25
	12-19	0	0	+ 44	0	+23	+ 7.2	+0.4	+ 58	+4	+ 6.6	- 58	+19	+ 3
	19-26	0	40	+ 10	+ 26	-40	+ 2.9	+0.2	+ 39	-1	+ 2.7	- 13	-39	-45
190	0-10	0	0	- 36	- 80	-87	-22.2	-0.3	- 33	-1	-21.9	- 47	-86	-34
	10-15	0	0	- 55	- 73	-43	+15.8	-0.4	- 78	-3	-15.7	+ 5	-40	- 3
246	0-10	0	0	+ 5	- 39	-34	- 6.1	0	+ 16	0	- 6.0	- 55	-34	-20
	10-15	0	0	- 56	- 74	-62	-14.8	-0.3	- 77	-2	-15.0	+ 3	-60	-24
75515	0-10	0	0	- 36	- 38	-61	-15.8	-0.3	- 28	-1	-15.2	- 10	-60	-24
	10-15	0	0	- 73	- 66	-74	-16.2	-0.4	-140	-3	-16.2	+ 74	-71	-33
92516	0-10	0	0	+ 42	+ 7	-48	+12.8	+0.4	+ 45	+3	+12.2	- 38	-51	-80
	10-18	60	0	+ 3	- 72	-83	+ 4.2	-0.2	- 37	-2	+ 3.8	- 35	-81	-90
382	0-11	41	0	+ 28	+ 22	-50	- 8.9	+0.1	+ 26	-1	- 8.2	- 4	-49	-29
	11-20	0	0	- 10	- 34	-35	-	-0.1	- 28	+1	-	- 6	-36	-
	20-30	0	30	+ 95	+255	-43	- 7.1	+1.2	+214	+4	- 6.7	+ 41	-47	-31
	30-41	0	0	+ 13	+ 8	-84	-16.6	-0.2	- 48	-1	-16.7	+ 56	-83	-43
	41-48	0	0	+ 4	- 8	-65	- 7.7	-0.1	- 8	+1	- 7.8	0	-66	-48
391	0-11	33	0	+ 29	+ 55	-66	- 9.1	+0.2	+ 17	-1	- 9.2	+ 38	-65	-43
	11-20	0	0	- 31	+ 10	-29	- 9.8	-0.2	- 20	+1	- 9.8	+ 30	-30	- 7
	20-30	0	30	- 34	- 87	-62	- 9.4	-0.2	- 39	-2	- 9.2	- 48	-60	-38
	30-41	0	0	+ 31	+ 33	-55	- 6.5	+0.2	+ 18	+2	- 6.7	+ 15	-57	-41
	41-48	0	0	+ 17	+ 53	-	- 9.6	+0.1	+ 41	+1	- 9.5	+ 12	-	-
404	0-11	35	0	+ 12	- 15	-60	- 5.6	-0.1	+ 6	-1	- 5.8	- 21	-59	-45
	11-20	0	0	- 38	-257	-53	- 1.8	+0.1	- 15	+2	- 1.8	-242	-55	-51
	20-30	0	30	+ 3	+ 70	-64	- 7.0	-0.2	- 9	-3	- 7.0	+ 79	-61	-44
	30-41	0	0	+ 50	+ 86	-74	+ 0.3	+0.4	+ 36	+2	+ 0.2	+ 50	-76	-76
	41-48	0	0	+ 69	+107	-51	+ 1.3	+0.6	+121	+2	+ 1.3	- 14	-53	-56

* Corrected for balance of NPN
** In excess of anabolism and catabolism of protein
External balances have been corrected for losses in vomitus

nary losses of this electrolyte. This differs of course from the hydrogen cycle resin studies in which reciprocal relationships could be postulated following a greater, *i.e.*, a three-fold rise in the amounts of potassium lost in stools.

D. Balance data: A significant proportion of the sodium released from the carboxylic cation exchanger and then absorbed was retained within the body despite the increases in urinary output described above. The data in Table III and Fig-

ure 3 indicate that this was associated, in contrast to the findings in the hydrogen resin studies, with an expansion of the chloride space.

DISCUSSION

Hydrogen resin therapy in dogs lowered serum sodium levels and raised the concentrations of serum chloride. The latter change is reminiscent of a similar response induced by acidifying diuretics (19, 20). The hyperchloremia was presumably initiated by the absorption of hydrogen ions set free from the resin with subsequent excretion in urine with anions other than chloride. The decrease in serum bicarbonate in these studies as a group represents, therefore, a metabolic acidosis and is attributable in a varying degree to a combination of hyperchloremia and a slight fall in fixed base. The lowered pH values support this view

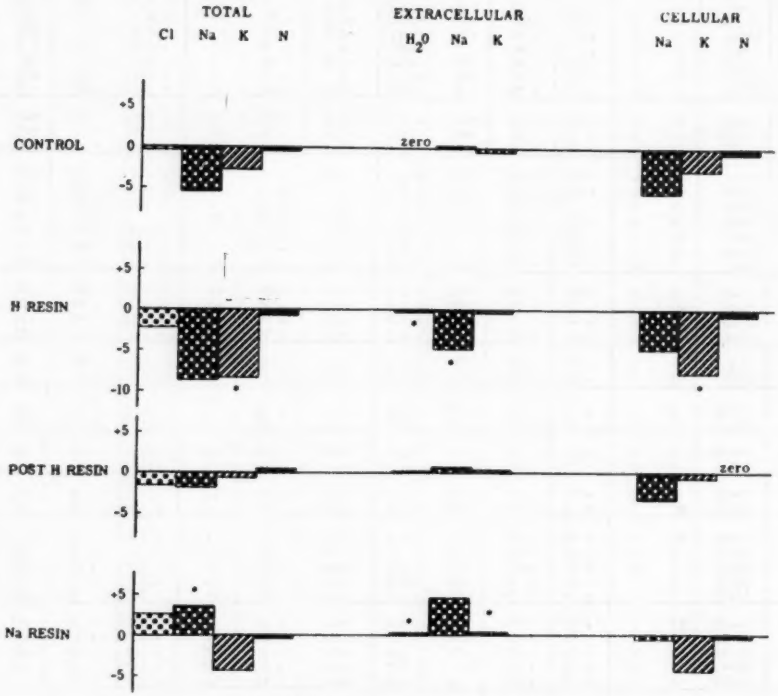

FIG. 3. AVERAGE DAILY BALANCES

The columns represent mean daily total (external), extracellular, and intracellular balances of chloride, sodium, and potassium in milli-equivalents and of nitrogen in grams during the indicated therapy. To observe the resin effects compare the balances during their administration to those during the control period. Asterisks denote mean values significantly different statistically from those characteristic of the control studies. Significant changes during H resin ingestion consisted of an approximately three-fold increase in the negative total balance of potassium. This cation was lost from the intracellular space both with and in excess of nitrogen since the cellular potassium represented has been corrected for the metabolism of protein. Sodium and water were lost from the extracellular or chloride space in the proportions in which they are usually present in this compartment. Balances during the post H resin period were similar to the control interval. The negative balances during both regimens reflect the inadequate dietary intake of the animals. Comparable diets were eaten, however, during all periods. In the Na resin studies exogenous sodium was retained in the expanded extracellular space and potassium increased slightly in this same compartment.

TABLE IV

Statistical evaluation of resin data

		Control periods			H resin periods			Post H resin periods			Na resin periods		
		Mean	No.	S. D.	Mean	No.	S. D.	Mean	No.	S. D.	Mean	No.	S. D.
Δ Serum	HCO_3 meq.	−0.1	22	2.3	−4.4<	13	3.8	+6.3>	8	3.9	+1.2	7	1.3
	Cl meq.	0.0	22	2.6	+3.7>	13	7.5	−5.2<	8	6.5	−3.6<	6	1.8
	Na meq.	+8.8	19	6.9	−4.5<	11	11.7	−3.7<	6	5.2	+4.3	6	7.1
	K meq.	0.0	22	0.7	−0.4	12	0.3	+0.4	8	0.7	−0.2	7	0.6
	H_2O l.	−0.001	17	0.009	+0.006>	10	0.007	0.000	7	0.015	+0.002	7	0.003
Stool	wgt. g./d.	145.5	18	92.3	169.3	14	133.9	167.8	9	84.3	201.4	7	89.3
	Cl meq./d.	3.7	17	2.0	3.4	14	2.4	4.2	9	2.2	4.0	7	2.2
	Cl meq./100 g.	3.0	19	1.1	1.9<	9	0.8	2.7	9	0.9	2.0<	7	1.0
	Cl meq./1.0 g. N	2.3	20	0.96	1.5<	9	0.8	1.5<	7	0.3	1.4<	7	0.8
	Na meq./d.	12.4	18	8.7	29.5>	14	17.7	15.8	9	6.3	71.4>	7	12.4
	Na meq./100 g.	8.4	18	2.2	21.7>	11	9.6	10.6>	9	3.1	39.9>	7	12.4
	Na meq./1.0 g. N	5.3	15	1.5	15.2>	10	8.6	5.8	7	0.9	29.8>	7	12.9
	K meq./d.	3.6	18	1.7	11.4>	14	5.9	4.7	9	1.6	7.9>	7	2.1
	K meq./100 g.	2.3	14	0.4	9.8>	11	6.6	2.8>	8	0.6	4.2>	7	1.0
	K meq./1.0 g. N	1.8	16	0.8	7.0>	10	5.7	1.5	6	0.3	3.1>	7	1.1
	N g./d.	2.0	17	1.4	2.5	14	2.3	3.0	8	1.4	3.0	7	1.8
	N g./100 g.	1.5	20	0.46	1.3	11	0.4	1.6	8	0.40	1.4	7	0.3
Urine	vol. ml./d.	157.3	18	74.6	298.5>	14	141.6	193.5	8	52.6	279.7>	7	33.2
	Cl meq./d.	32.8	18	14.0	24.3	13	15.4	42.4	8	6.4	42.0	7	6.7
	Na meq./d.	30.6	18	16.2	5.6<	11	3.7	37.8	8	8.4	109.9>	7	17.8
	K meq./d.	21.5	15	5.7	14.5<	13	11.0	20.6	8	4.3	24.1	7	9.5
	N g./d.	5.2	18	2.1	4.7	13	1.9	5.7	9	1.2	5.2	7	1.4
Δ Body wgt.	Kg./d.	−0.004	18	0.033	−0.081<	14	0.083	+0.025	8	0.043	−0.031	7	0.057
Balances:													
External Cl	meq./d.	−0.6	17	3.0	−2.2	14	7.4	−1.4	8	3.4	+2.4	7	4.3
External Na	meq./d.	−5.2	17	5.4	−8.4	14	7.9	−1.6	8	7.2	+3.7>	7	8.7
External K	meq./d.	−2.3	17	4.5	−8.2<	14	5.1	−0.5	9	4.4	−4.1	7	2.2
External N	g./d.	−0.29	16	0.96	−0.91	13	1.44	+0.02	8	0.83	−0.18	7	0.49
Extracell. H_2O	l./d.	0.00	17	0.02	−0.03<	14	0.05	+0.01	9	0.03	+0.03>	7	0.05
Extracell. Na	meq./d.	+0.3	15	3.2	−4.9<	13	7.8	+0.5	9	5.7	+4.5	7	9.0
Extracell. K	meq./d.	−0.1	16	0.3	−0.2	12	0.2	+0.2	8	0.3	+0.3>	6	0.4
Cell. Na	meq./d.	−5.4	16	6.5	−4.9	13	7.1	−3.2	8	2.8	−0.9	7	9.0
Cell. K	meq./d.	−2.8	17	3.9	−7.9<	14	5.0	−0.6	9	4.3	−4.2	7	2.0
Cell. N	g./d.	−0.30	16	0.93	−0.90	13	1.44	0.00	8	1.07	−0.17	7	0.48
Cell. *K	meq./d.	−3.0	15	3.6	−5.2	12	3.2	+0.7	8	4.7	−3.8	7	1.6

No.—Number of replicates

S. D.—Standard Deviation—$\sqrt{\frac{\text{squared sum of deviations from mean}}{N-1}}$

>—Deviation above control mean is statistically significant (p for t-test is <0.05)

<—Deviation below control mean is statistically significant (p for t-test is <0.05)

*K—K exchanges in excess of the anabolism or catabolism of N

as does the failure to observe comparable changes following ingestion of the sodium form of the resin.

It seems clear that the action of cation exchange resins in the hydrogen cycle is analogous to the effects of administration of ammonium chloride (19, 20), and similar acidifying substances, with respect to production of metabolic acidosis and water diuresis. In the case of the resin, however, the renal excretion of sodium and potassium was not accelerated in contrast to the striking augmentation of their urinary outputs by so-called acidifying diuretics (19, 20). This failure of augmented excretion of sodium and potassium may be a reflection of increased stool output of these ions. Furthermore urinary excretion of potassium and sodium although reduced by the resin might have been even lower if acidosis had not occurred.

Nevertheless data of the present study constitute evidence against the hypothesis that the water diuresis produced by acidifying substances is necessarily related to augmented renal excretion of sodium or potassium.

Despite the unequivocal character of the two-fold or greater rise in stool sodium during hydrogen resin therapy, and the statistically significant decreases in serum as well as extracellular sodium, the external balances of this electrolyte were not altered. This is in great measure and perhaps entirely attributable to the profound reduction in urinary sodium. This adjustment occurring regularly would obviously make it difficult if not impossible to produce salt depletion. It also suggests that even with the comparatively large doses used in these studies the resin seldom removes endogenous sodium in amounts sufficient to produce negative external balances of this cation. It should be pointed out, however, that in the diets employed in this study large amounts of sodium were ingested. No data are available to indicate whether or not depletion of endogenous sodium could be achieved by using the hydrogen form resin during regimens sharply restricted in sodium.

Similarly, as in the case of the sodium ion, the daily urinary losses of potassium declined as stool excretion of this cation rose several fold during hydrogen resin therapy. It should be emphasized, however, that in absolute terms more potassium than sodium was lost in stools during hydrogen resin ingestion. Since the diets employed and the gastrointestinal secretions contained preponderantly greater amounts of sodium than of potassium, it is obvious that the larger losses of potassium reflect the recognized greater affinity of the carboxyl cation exchangers for this element over sodium. The large increase in stool potassium during resin therapy, together with a proportionately smaller decrease in the concomitant urinary losses of potassium, resulted in negative balances of body potassium. The losses represented decreases in cell potassium, since extracellular potassium did not change. The accompanying deficits of cell nitrogen were of insufficient magnitude to account for all of the potassium lost from cells. It is clear, therefore, that potassium was lost in these experiments both with and in excess of the catabolism of cell protein. This was not accompanied, presumably because the experimental periods were short, by any of the usual clinical indices of potassium depletion.

It has been previously noted in studies from this and other laboratories that such negative balances of potassium may be associated with an apparent entry of sodium into the cell (12, 14, 15). The mean daily change in cell sodium, however, cannot be established as statistically different from the control values. It has already been pointed out earlier that in our studies with the hydrogen form of the resin cell potassium deficits developed during a metabolic acidosis, a state which may result in transfers of sodium out of cells (21–23). These stimuli toward divergent movements of this ion may therefore have cancelled one another.

Finally it is evident that although administering the resin in the sodium cycle does raise stool potassium without concomitant acidosis, these increments are of lesser magnitude than those produced by the hydrogen resin and are not accompanied by decreases in serum potassium concentration, nor in the mean daily urinary potassium excretion. Potassium balances remain unaffected. It should be reiterated that use of this particular form of the exchanger results in considerable absorption and retention of the released sodium. This latter development results in positive balances of the electrolyte and expansion of the volume of the extracellular fluid as measured by the chloride space.

SUMMARY AND CONCLUSIONS

1. Administration of a hydrogen cycle carboxylic cation exchange resin to dogs, 30 to 60 g./day for seven to 11 days, produced a statistically significant decrease in serum sodium, a rise in serum chloride and a metabolic acidosis characterized by a fall in serum carbon dioxide content and pH.

2. During therapy with this resin, increased amounts of sodium and of potassium were lost in stools without alteration in stool chloride or nitrogen excretion.

3. With hydrogen resin ingestion urine volumes rose with a decrease in urinary concentrations of sodium, potassium, chloride and nitrogen; the daily output of sodium and of potassium fell si-

multaneously with the increased losses in stools.

4. Hydrogen cycle resin administration lowered the total amount of sodium in the chloride space without producing any statistically detectable change in the external balances of this cation.

5. Negative external and cell balances of potassium increased significantly during hydrogen resin therapy. These were related in part to the particular affinity of the resin for potassium and in part to a less than completely compensatory decrease in the urinary excretion of this element.

6. Administration of the same carboxylic cation exchanger in the sodium rather than the hydrogen form resulted in an extracellular retention of some of the released sodium despite increased losses of this ion in stools and in urine.

7. During sodium cycle resin therapy a statistically significant increase in the stool losses of potassium occurred, smaller in magnitude, however, than that observed with the hydrogen cycle exchanger and unaccompanied by any detectable change in the daily urinary output or in the daily balance of potassium.

8. In contrast to the hydrogen form of the exchanger administration of the sodium charged resin did not result in an acidosis but did produce a decrease rather than an increase in serum chloride, possibly as a manifestation of the increased urinary sodium losses.

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ADDENDUM

The data were calculated in the following manner:

I. External Balance: $b = I - O$ where b = external balance; I = intake; and O = total output including the amounts of the substance in urine, stool, vomitus and in the serum contained in the blood withdrawn.

II. In order to apportion the external balance between cells and extracellular fluid, the amount in the extracellular fluid was calculated and then subtracted from the external balance.

A. Conversion of serum values of electrolytes into concentrations in extracellular water employing corrections for Donnan effect and for water content of serum.

$$\frac{[Cl]_s}{(0.95)[H_2O]_s} = [Cl]_{ECW}$$

$$\frac{[Na]_s \times (0.95)}{[H_2O]_s} = [Na]_{ECW}$$

$$\frac{[K]_s \times (0.95)}{[H_2O]_s} = [K]_{ECW}$$

where $[\ ]_s$ = serum concentration in meq./l.

0.95 = correction for Donnan effect

$[H_2O]_s$ = water concentration of serum in Kg./l.

B. Calculation of extracellular water changes were based on the chloride space, assuming that chloride was confined to this compartment, and that the initial extracellular fluid made up 20% of the body weight in a normally hydrated subject.

$$[Cl]_{ECW_1} \times (ECW)_1 + bCl = [Cl]_{ECW_2} \times (ECW)_2$$

Rearranging:

$$(ECW)_2 = \frac{[Cl]_{ECW_1} \times (ECW)_1 + bCl}{[Cl]_{ECW_2}}$$

where $[Cl]_{ECW_1}$ = chloride concentration in meq./l. in extracellular fluid at start of period

$[Cl]_{ECW_2}$ = chloride concentration in meq./l. in extracellular fluid at end of period

$(ECW)_1$ = assumed extracellular volume at start obtained by multiplying body weight in kilograms by 0.20

$(ECW)_2$ = unknown extracellular volume at end

bCl = external balance of Cl in the period

C. Changes in extracellular Na and K represent the difference between final and initial amounts of these substances in this compartment.

$$[Na]_{ECW_2} \times (ECW)_2 - [Na]_{ECW_1} \times (ECW)_1 = \Delta\ Na_{ECW}$$

$$[K]_{ECW_2} \times (ECW)_2 - [K]_{ECW_1} \times (ECW)_1 = \Delta\ K_{ECW}$$

where $[\ ]_{ECW_2}$ = concentration in meq./l. in extracellular fluid

$(ECW)_1$ = initial extracellular fluid

$(ECW)_2$ = final extracellular fluid

Δ ECW = balance of the substance in extracellular fluid

D. Cellular balances indicate the difference between the external and the extracellular balance.

$$b\ Na - \Delta\ Na_{ECW} = \Delta\ Na_{ICW}$$

$$b\ K - \Delta\ K_{ECW} = \Delta\ K_{ICW}$$

where b = external balance

Δ_{ECW} = extracellular balance

Δ_{ICW} = intracellular balance

E. Determination of the intracellular balance of potassium which is in excess of the amount associated with nitrogen requires correction of this balance for the amount associated with nitrogen metabolism. Since 2.38 meq. of K are associated with each gram of intracellular nitrogen this is simply calculated. Nitrogen balances, however, must be corrected for NPN changes since these obviously alter the observed external balance. For example assuming that the NPN is distributed throughout total body water, and the body water comprises 65% of the body weight the following formulae are applicable:

$$\frac{(\text{Body wgt.})(0.65) \times \Delta\ NPN \times 10}{1000} = b\ NPN$$

$$b\ N - b\ NPN = b'N$$

where Δ NPN = change in NPN in mgm. % (with sign)

b NPN = change in N balance associated with change in NPN

b N = external balance of N

b'N = balance of N corrected for NPN change

The importance of this correction is illustrated: if we have a 60 Kg. subject whose NPN changes from 40 mgm. % to 30 mgm. %, the correction will be as large as −3.9 g. of N. If the NPN in this person went from 30 to 50, then the b NPN would equal +7.8 g. N. This will, of course, significantly alter the external balance of N.

In order to determine the intracellular K balance which does not represent K moving with protein metabolism the following calculations must be performed:

$$(b'N) \times (2.38) = K_N$$

where K_N = K associated with protein metabolism

$$\Delta\ K_{ICW} - K_N = \Delta\ K'_{ICW}$$

where $\Delta\ K'_{ICW}$ = change in intracellular K in excess of the K associated with N metabolism

The amounts of Na associated with N metabolism are so small that this correction may be omitted.

BIOCHEMICAL CHANGES ACCOMPANYING THE INGESTION OF A CARBOXYLIC CATION EXCHANGER IN THE HYDROGEN, AMMONIUM, SODIUM, POTASSIUM, OR CALCIUM FORM

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Preceding studies from this laboratory have defined certain changes in body fluids in dogs (1) and, in preliminary form, in human subjects (2, 3) accompanying the ingestion of carboxylic cation exchangers in the hydrogen cycle. In general, hyperchloremia appeared in both groups, the serum bicarbonate was lowered, and the stool output of sodium and potassium increased whereas chloride and nitrogen excretion did not change. In this paper further studies of the resins in various forms in human subjects are reported as a basis for a more adequate understanding of factors contributing to or limiting the clinical utility of these compounds.

MATERIALS AND METHODS

Carboxylic cation exchangers in the hydrogen, ammonium, potassium, sodium, or calcium form have been tested in children and adults with a variety of diseases. Selection of the patients was based primarily on willingness and ability to cooperate in the study. Edema was present in some. The experimental procedures, analytical techniques, and statistical treatment have been detailed in the animal studies mentioned earlier (1). The patients were usually but not invariably maintained on a milk formula or on a diet not rigidly restricted as to sodium content. Again it should be emphasized that all stools included in the study were formed.

RESULTS

A. Effects of hydrogen or ammonium cycle resin ingestion

From Tables I and II and the summary of mean changes in Figure 1, it is evident that the alterations in serum constituents accompanying comparable average daily intakes of these two agents, 39.7 and 38.3 g. respectively, are essentially indistinguishable. Hyperchloremia, and lowered serum bicarbonate and potassium values developed in both groups of subjects without a statistically significant change in serum sodium. Other measured constituents of serum or blood were not affected. The mean output of sodium and of potassium per day, per unit of stool mass, and per gram of stool nitrogen (Tables III, IV, and Figure 2) rose without alteration in the excretion of chloride or nitrogen via this route.

Ingestion of the hydrogen form resin was accompanied by an increase in the average daily urine volumes without statistically significant variation in the total daily output of the various urinary constituents (Table V). In general the external balances of chloride and of sodium (Table VI) remained positive during resin therapy except in those periods in patients WK, CSc, and GDe, when edema was being delivered and in VG when the body weight was decreasing on a reducing diet. Usually simultaneous declines were recorded in both the chloride space and the extracellular sodium of these subjects. Cell nitrogen balances remained positive during resin therapy save for the obese patient, VG, who was on a limited caloric intake. With but few exceptions losses of potassium from cells coincided with and were induced by hydrogen form resin therapy. The most striking losses occurred in CSc. In the experiments with the ammonium form of the resin it is to be noted that cell potassium balances remained positive during resin therapy (Table VII). Since the stool excretion of this element had increased significantly it is obvious that the intake of this electrolyte had been more than adequate to prevent negative balances.

It is to be noted in addition that in patient SB who received cortisone as well as the ammonium form of the resin a decrease in serum carbon dioxide content and abnormally low serum potassium concentrations occurred (Table II) together with

marked increases in stool sodium and potassium excretion (Table IV and Figure 2).

B. Changes during sodium or potassium cycle resin administration

Neither of these resins produced any statistically significant changes in the mean values for carbon dioxide content, chloride, sodium, potassium, calcium or water, although serum inorganic phosphorus rose slightly when the potassium form of the resin was ingested (Figure 1, Tables VIII and IX). On the other hand in subjects CSt and CSc (Table IX) the serum potassium rose to hyperkaliemic levels, 6.1 meq./l., during therapy with the cation exchanger in the potassium form. In addition in CSc the extracellular potassium increased. Comparable data are not available for the other patient.

TABLE I

Body weight and analyses of blood and serum in subjects receiving the cation exchanger in the H cycle

Subject	Time	Therapy	Body Wgt.	Blood		Serum							
(Age-Sex)	(Days)	(g./d.)	(kg.)	Sugar (mgm%)	NPN (mgm%)	HCO_3 (meq./l.)	Cl (meq./l.)	Na (meq./l.)	K (meq./l.)	Ca (mgm%)	P (mgm%)	H_2O (g./l.)	Protein (g.%)
VW	0	0	32.6	325	34	23.4	97.8	136	4.8	10.2	5.2	928	8.0
12 M	0-3	0	33.0	-	34	25.4	95.4	141	5.0	10.8	5.3	930	7.5
Diabetes	3-6	0	32.6	119	32	25.9	105.6	144	4.4	9.0	6.1	935	6.7
	6-9	25	32.8	288	33	21.9	106.1	142	4.3	9.5	4.9	929	7.2
	9-12	35	33.2	234	32	20.4	104.8	138	4.6	-	-	925	7.9
CAS	0	0	41.6	166	35	25.0	103.4	145	4.5	-	5.7	929	7.4
9 F	0-3	0	41.6	-	31	25.8	102.8	143	4.7	9.8	5.2	926	7.9
Diabetes	3-6	0	40.8	-	34	25.0	104.5	147	3.9	9.2	4.8	929	7.7
	6-9	25	40.6	-	31	22.6	108.3	144	5.3	9.6	5.2	934	7.3
	9-12	35	41.1	131	32	20.7	108.9	141	4.1	-	5.6	923	8.1
VG	0	0	144.0	72	29	19.7	105.2	147	4.5	10.3	3.8	-	7.5
14 F	0-3	0	145.1	68	32	21.8	105.6	156	4.8	10.1	-	-	7.3
Obesity	3-6	0	144.6	75	27	22.9	102.1	142	4.3	9.9	3.5	931	-
	6-9	0	143.1	78	24	22.6	100.8	139	4.3	10.8	3.9	930	7.9
	9-12	32	141.5	80	24	18.7	106.9	135	4.5	-	3.3	-	7.9
	12-15	32	141.0	72	25	17.5	110.2	141	4.2	-	-	-	7.2
	15-18	32	139.8	80	25	19.5	107.7	139	3.9	10.3	3.9	926	8.2
	18-21	0	138.2	-	33	22.8	103.5	145	4.3	10.3	4.1	930	8.4
	21-24	0	136.8	-	30	23.7	101.0	142	4.7	10.8	4.8	926	8.1
	24-27	0	135.5	-	33	21.6	98.5	142	3.9	11.0	-	924	7.8
JMc	0	0	44.0	257	32	22.8	101.4	141	-	-	-	931	7.3
15 M	0-3	0	43.6	231	31	22.9	103.7	143	4.4	-	5.1	932	-
Diabetes	3-6	0	-	266	29	22.9	102.4	136	4.8	-	-	-	6.8
	6-9	40	-	167	33	18.5	105.9	143	3.7	-	-	927	-
	9-12	40	-	249	29	16.1	108.1	138	4.0	10.8	4.8	923	7.2
EMc	0	0	42.0	171	36	25.9	104.7	141	4.4	9.4	4.6	932	7.1
11 F	0-3	0	42.0	150	35	21.7	108.9	145	4.5	-	-	929	-
Diabetes	3-6	0	42.0	207	31	24.1	105.4	145	5.0	9.5	4.5	924	6.8
	6-9	40	42.0	166	31	18.2	111.8	143	3.7	-	-	931	-
	9-12	40	42.2	209	34	16.9	109.2	143	3.7	9.7	4.5	929	7.9
WK	0	0	62.9	70	40	28.3	100.5	142	4.6	11.0	3.8	934	6.5
57 M	0-2	32	61.3	80	49	23.2	106.7	139	4.4	10.6	3.4	934	6.3
Cong.	2-4	32	59.0	84	51	22.4	106.5	138	3.7	9.8	3.3	-	7.0
Failure	4-6	32	58.3	93	48	20.1	104.3	141	4.0	-	4.3	-	7.6
	6-8	32	57.5	83	48	19.3	104.8	142	4.4	-	3.9	934	7.0
	8-9	32	57.3	-	46	20.2	106.4	141	3.9	10.1	-	922	-
	9-13	0	58.2	87	47	25.9	101.8	143	4.1	10.2	4.1	930	7.4
	13-15	0	59.3	-	44	24.7	102.4	142	4.7	-	4.4	934	6.9
CBc	0	0	48.9	87	33	22.2	110.4	142	5.2	11.2	4.8	939	6.3
33 F	0-3	0	49.3	88	32	25.4	104.8	137	5.0	9.7	5.4	941	5.9
C-V Dis.	3-6	0	50.9	-	31	26.4	104.4	144	4.7	9.6	5.8	941	6.2
	6-9	32	49.8	75	29	20.5	107.8	141	4.4	-	6.2	938	-
	9-12	32	49.1	-	29	23.6	106.5	142	4.1	9.6	5.2	939	6.6
	12-15	0	48.5	-	31	23.4	101.9	139	4.9	-	-	928	-
	15-19	0	47.9	-	-	27.0	103.6	142	5.4	-	-	936	-
CDe	0	0	67.7	-	81	21.5	100.6	145	5.2	9.2	6.3	938	5.5
34 M	0-5	30	57.8	-	87	12.2	112.3	139	6.8	9.0	9.1	930	6.3
Chr.	5-10	0	56.4	-	80	14.4	108.6	135	5.4	-	7.3	931	6.2
Nephritis	10-15	21	57.6	-	76	13.7	115.9	142	4.3	9.5	6.2	937	5.9
	15-19	20	56.6	87	73	13.7	113.8	145	4.0	8.7	6.3	936	6.4
	19-25	60	55.8	-	62	13.2	116.3	140	3.5	7.8	5.8	941	5.9

TABLE II

Body weight and analyses of blood and serum in subjects receiving cation exchanger in the NH_4 cycle

Subject (*Age–Sex*)	Time (*Days*)	Therapy (*g./d.*)	Body Wgt. (*kg.*)	Blood		Serum							
				Sugar (*mgm. %*)	NPN (*mgm. %*)	HCO_3 (*meq./l.*)	Cl (*meq./l.*)	Na (*meq./l.*)	K (*meq./l.*)	Ca (*mgm. %*)	P (*mgm. %*)	H_2O (*g./l.*)	Protein (*g. %*)
JF	0	0	69.5	—	35	25.7	95.9	138	4.5	9.5	3.2	929	7.5
29 M	0–6	40	67.4	124	34	27.5	100.2	150	4.5	9.8	3.5	929	7.8
Diabetes	6–12	0	66.6	—	41	30.1	98.0	149	4.5	10.0	3.6	925	8.1
	12–18	40	67.0	108	38	23.7	104.9	145	5.3	9.7	3.5	925	7.9
	18–24	0	68.9	69	32	28.1	104.0	147	5.0	9.5	4.4	934	7.3
CS	0	0	60.2	—	33	26.3	108.8	144	4.3	8.4	2.6	935	6.6
54 M	0–6	40	—	—	36	14.4	114.5	144	4.1	8.8	2.3	931	7.2
Arthritis	6–7	0	—	—	—	23.0	110.4	144	3.7	—	—	—	—
	7–12	0	—	—	31	27.6	101.7	145	4.4	8.9	2.1	938	—
CSc	0*	*	48.7	—	38	29.4	90.8	142	6.1	8.8	5.0	939	6.3
33 F	0–7	8	48.0	—	39	24.4	97.0	140	4.4	—	—	944	—
C-V dis.	7–13	40	48.4	—	41	22.8	101.2	153	3.8	—	3.8	933	—
	13–19	0	52.7	90	35	26.6	94.5	136	4.3	8.8	4.5	941	6.1
SB†	0	†	28.0	70	36	23.7	106.5	148	4.6	—	—	934	—
7 F	0–3	40	28.3	—	—	28.7	99.9	150	2.4	10.1	3.6	938	—
Rh. Fev.	3–6	40	27.9	65	36	30.2	97.1	144	3.4	9.1	3.5	937	—
	6–9	40	28.1	76	29	28.1	101.4	145	2.8	—	—	934	—
	9–12	40	28.0	78	30	30.1	99.1	145	2.5	—	4.0	—	6.5
	12–15	40	28.5	59	32	—	96.5	144	2.9	—	3.1	—	6.7
	15–18	40	—	61	29	27.8	100.7	150	4.8	—	4.0	936	7.0
	18–21	40	—	92	36	20.3	109.7	148	4.2	—	4.4	—	—
WY	0	0	74.1	—	68	23.2	107.7	138	5.1	9.3	5.0	924	7.0
45 M	0–6	40	71.7	160	63	16.2	108.4	143	3.8	8.5	4.8	921	7.7
Diabetes	6–7	0	—	—	63	17.5	111.5	144	4.4	—	—	—	—
	7–12	0	71.8	172	55	20.4	109.4	140	4.3	9.6	4.7	929	7.3
EMc	0	0	—	—	42	27.2	107.4	144	4.5	9.1	3.3	926	7.3
71 F	0–6	40	—	203	46	11.8	117.2	144	4.0	8.9	3.0	927	8.0
Diabetes	6–7	0	—	—	42	15.2	115.5	145	4.0	—	—	—	—
DY	0‡	‡	30.4	67	44	23.1	108.6	141	3.7	6.7	5.0	936	3.7
12 M	0–4	35	31.4	—	33	19.7	113.7	140	3.1	—	4.2	938	3.5
Nephrosis	4–10	0	31.4	—	36	20.5	110.1	139	4.0	7.3	4.5	933	3.6
WG	0	0	32.4	62	35	25.8	104.1	135	4.5	11.5	5.4	936	6.8
12 M	0–5	0	30.4	80	43	21.7	106.7	—	—	—	5.4	915	—
Gl. Neph.	5–10	0	28.8	—	35	24.9	97.4	140	4.9	—	5.0	921	—
(healed)	10–15	0	30.1	75	36	27.2	100.4	138	5.4	9.9	4.8	927	8.3
	15–20	0	30.1	—	35	26.6	105.1	140	4.4	9.5	4.6	930	7.7
	20–26	38	30.0	—	37	26.6	105.0	141	3.8	—	—	—	—
	26–31	0	29.8	—	44	26.6	101.5	137	4.0	10.0	4.6	925	7.8

* End of K resin period.
† Patient receiving cortisone throughout study, 100 mgm./day for 40 days.
‡ End of K resin period.

Ingestion of the sodium cycle resin increased the stool output of potassium and of sodium (Table X and Figure 2). Similarly, on an intake of the potassium cycle resin, stool potassium and, to a lesser extent, stool sodium increased (Table XI and Figure 2). In each group of experiments, some of the cation, either sodium or potassium, ingested with the resin was released and entered the body fluids. Though daily urinary excretions of the particular cation under scrutiny were quite high, positive external balances were recorded (Tables XII and XIII). In the case of the sodium resin, the absorbed cation, sodium, remained primarily in the extracellular phase (Subjects EB, JV, and VB). Potassium released from the resin on the other hand was retained in the body and entered the cellular phase in patient RC (Table XIII). Patients WG and CSc, however, excreted

this cation in both urine and stool and lost it from cells.

C. Studies during calcium cycle resin

Insofar as can be determined by inspection of Table XIV or statistical comparison of mean values (Figure 2) this resin failed to influence either the stool output of chloride, or nitrogen but did raise to a slight extent the stool sodium in all categories and stool potassium in the per day and per gram of nitrogen groupings. It would appear, therefore, that attachment of this divalent cation to the carboxylic exchanger renders it less effective from the point of view of affecting stool excretion of sodium and potassium. Furthermore there is no evidence of any consistent and significant change in either the individual values or the means of most of the measured serum constituents, includ-

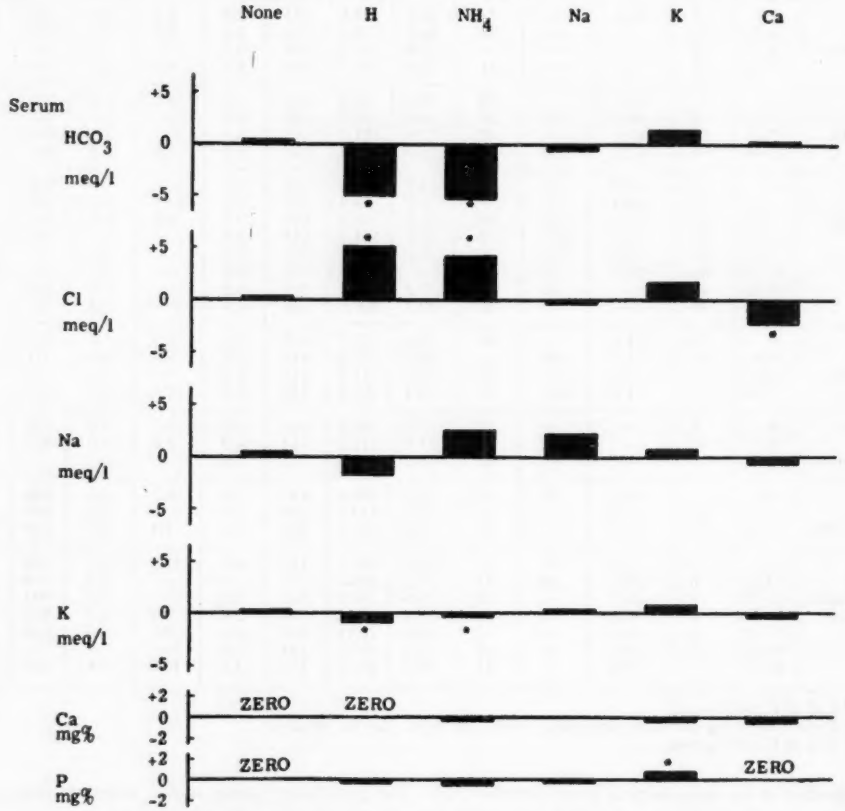

FIG. 1. SERUM ELECTROLYTE CONCENTRATIONS WITH AND WITHOUT RESIN THERAPY

The blocks represent mean alterations in serum constituents between the onset and the end of each of the regimens indicated at the head of the individual columns. The chemical abbreviations stand for the form of resin ingested. Asterisks identify statistically significant differences from the changes in the control values ("p" for the "t" test equals 0.05 or less). Without resin therapy serum constituents listed on the left varied but little. Treatment with H or NH_4 forms produced acidosis and hyperchloremia and lowered serum potassium levels. Ingestion of the Na form did not produce any significant changes. Serum inorganic phosphorus rose during administration of the K cycle, and serum chloride fell when the Ca form was ingested.

TABLE III

Intake data and urine and stool output in subjects receiving the cation exchanger in the H cycle

Subj.	Time	Therapy	Intake					Urine					Stool				
	(days)	(g./d.)	Fluid (l.)	Cl (meq.)	Na (meq.)	K (meq.)	N (gm.)	Vol. (l.)	Cl (meq.)	Na (meq.)	K (meq.)	TN (gm.)	Wgt. (gm.)	Cl (meq.)	Na (meq.)	K (meq.)	N (gm.)
VV	0-3	0	7.36	290	259	230	33.5	3.88	253	221	200	27.7	643	7	7	102	5.6
	3-6	0	7.11	215	180	257	37.4	3.18	115	115	195	28.3					
	6-9	25	8.96	215	180	257	37.4	5.91	132	87	189	25.4	563	8	118	319	5.1
	9-12	35	9.28	215	180	257	37.4	8.30	183	91	91	29.2					
CAS	0-3	0	6.84	512	481	230	33.6	3.48	447	470	170	25.0	55	1	3	9	0.8
	3-6	0	6.80	545	512	245	35.8	2.73	408	459	177	24.9					
	6-9	25	7.79	568	534	256	37.3	2.79	389	340	107	23.7					
	9-12	35	7.44	568	534	256	37.3	4.25	509	482	81	29.3	197	3	22	136	1.4
VG	0-3	0	5.55	246	231	111	16.2	1.10	215	188	32	16.2					
	3-6	0	4.58	271	254	122	17.8	0.50	136	139	19	5.6	371	3	140	87	5.0
	6-9	0	3.58	216	203	97	14.2	1.00	233	244	82	11.9					
	9-12	32	4.42	205	193	93	13.5	1.49	204	187	86	13.1					
	12-15	32	4.46	225	192	101	14.8	1.65	240	104	53	14.9	-	0.4	149	104	1.0
	15-18	32	6.12	250	235	113	16.5	4.58	551	280	50	22.7					
	18-21	0	4.40	50	3	120	14.2	2.60	225	98	28	16.2					
	21-24	0	3.40	41	2	99	11.7	3.25	107	36	50	19.4	89	0	28	26	1.0
	24-27	0	4.28	47	3	115	13.5	2.80	50	57	60	15.1					
JMc	0-3	0		Full	diab.	diet		4.25	614	587	193	37.1	708	5	57	83	10.0
	3-6	0		"	"	"		3.75	515	638	110	34.9					
	6-9	40		"	"	"		7.04	716	929	232	43.2					
	9-12	40		"	"	"		3.20	299	173	69	32.0	775	5	174	334	8.8
KMc	0-3	0		Full	diab.	diet		3.76	458	508	140	38.5	494	5	11	44	7.9
	3-6	0		"	"	"		1.85	249	249	94	22.4					
	6-9	40		"	"	"		5.62	516	337	188	42.9					
	9-12	40		"	"	"		4.22	353	146	66	37.0	905	4	351	283	6.6
WK	0-2	32	6.47	83	5	200	23.6	3.96	132	82	84	14.1					
	2-4	32	6.25	89	5	216	25.4	5.38	190	105	93	18.2					
	4-6	32	7.50	89	5	216	25.4	3.57	98	31	51	17.1	451	6	88	147	4.1
	6-8	32	5.79	78	5	189	22.3	4.05	92	24	38	20.0					
	8-9	32	3.02	44	3	108	12.7	1.70	38	5	9	8.6					
	9-13	0	13.48	180	11	437	51.5	5.20	154	50	73	47.1					
	13-15	0	6.71	89	5	216	25.4	0.48	15	3	7	5.7	104	3	9	17	2.6
CSc	0-3	0	8.32	556	525	230	33.6	4.12	446	269	184	26.8					
	3-6	0	10.26	567	532	256	37.3	4.75	442	370	206	26.2	240	5	14	147	2.7
	6-9	32	11.70	567	532	256	37.3	9.70	650	613	247	28.1					
	9-12	32	12.95	649	609	293	42.7	9.80	588	491	138	37.8	1092	9	527	523	9.8
	12-15	0	8.33	112	7	272	32.1	5.80	247	101	163	29.3					
	15-19	0	12.43	166	10	404	47.6	8.40	249	88	300	37.9	288	3	93	129	3.9
SDe	0-5	30	18.63	309	259	369	53.9	5.35	262	317	139	22.1	2466	13	92	94	5.6
	5-10	0	16.76	304	256	364	53.1	4.90	192	162	126	22.5	1443	5	18	42	4.8
	10-15	21		Full	- diet			9.25	377	324	365	-	428	1	12	122	4.9
	15-19	20		("Salt-free")		diet		9.50	346	319	137	36.7	317	1	8	98	3.8
	19-25	60		Full	diet			17.40	870	736	197	53.6	548	11	63	230	6.8

ing calcium and phosphorus (Table XV and Figure 1). The chloride concentration, however, fell approximately 2 meq./l. in all patients without other change. Balance data, however, were not consistently altered in VB or JF (Table XVI).

D. Comparison of the efficiency of the various resin forms

Mean stool excretion of sodium and potassium per gram of resin was determined during administration of the hydrogen, ammonium, potassium, sodium, and calcium forms of the cation exchanger in the experiments in which sodium was not rigidly withheld. The few studies in which the diet was almost completely free of sodium are included in the tables, but excluded from the means, to illustrate the decrease in efficiency of the hydrogen and ammonium forms under such circumstances. For simplicity the calculations are omitted, but the findings can be summarized briefly.

The hydrogen, ammonium, and potassium forms of the resin removed equivalent amounts of sodium plus potassium in stools (1.5, 1.9, and 1.9 meq./g. respectively). Mean stool sodium averaged 0.4 to

TABLE IV

Intake data and urine and stool output in subjects receiving cation exchanger in the NH_4 cycle

Subj.	Time	Therapy	Intake					Urine					Stool				
	(Days)	(g./d.)	Fluid (l.)	Cl (meq.)	Na (meq.)	K (meq.)	N (g.)	Vol. (l.)	Cl (meq.)	Na (meq.)	K (meq.)	TN (g.)	Wgt. (g.)	Cl (meq.)	Na (meq.)	K (meq.)	N (g.)
JF	0–6	40	Full diab. diet					17.60	1442	1045	396	90.6	73	0.3	10	25	2.4
	6–12	0	23.23	521	436	622	90.6	12.15	401	343	274	75.6	286	0.3	30	122	2.6
	12–18	40	20.14	496	416	592	86.3	8.60	156	26	218	86.1	611	4	45	214	3.4
	18–24	0	Full diab. diet					9.24	1850	1862	191	74.1	495	13	44	102	3.3
CS	0–6	40	Full diet					7.00	735	367	189	46.6	704	18	398	130	4.6
	6–12	0						2.50	285	152	54	36.8	782	51	88	67	8.5
CSc	0–7	8	14.92	281	234	336	49.0	8.60	0	0	305	63.0	—	—	—	—	—
	7–13	40	"Salt-free" diet					8.10	26	3	81	—	910	12	48	240	8.1
	13–19	0						8.80	19	0	62	41.9	212	3	9	44	1.9
SB	0–3	40	Full diet					4.00	408	185	81	40.3	1228	21	181	266	9.4
	3–6	40						4.97	434	240	55	34.6					
	6–9	40						4.13	369	224	103	—	—	—	—	—	—
	9–12	40						4.52	460	256	39	33.1	1130	13	293	347	8.4
	12–15	40						4.26	466	318	57	45.7	642	3	195	162	6.2
	15–18	40						5.82	506	640	54	46.0	670	3	192	232	6.9
	18–21	40						4.66	301	—	—	27.7					
	21–23	40						2.02	83	—	—	—	259	3	94	50	2.9
WY	0–6	40	11.89	261	219	311	45.4	6.40	95	85	160	41.4	2109	25	258	134	13.0
	6–12	0	13.02	267	224	318	46.4	7.00	298	186	161	48.4	850	3	17	80	8.0
EMc	0–6	40	Full diab. diet										346	1	118	166	2.4
DY	0–4	35	Full diet					4.10	163	94	189	50.0*	570	3	123	132	5.7
	4–10	0	11.03	146	9	354	65.0	7.05	338	197	270	58.0*	1171	11	26	48	6.3
WG	0–5	0	12.64	223	13	542	64.0	7.88	386	272	259	40.1	470	5	6	96	5.2
	5–10	0	13.58	233	14	566	66.8	7.25	251	54	338	48.9	299	3	9	51	3.7
	10–15	0	13.80	233	14	566	66.8	9.19	275	21	391	52.7	534	6	3	90	5.9
	15–20	0	12.95	233	14	566	103.8	7.72	268	68	363	56.4	475	5	8	77	6.8
	20–26	38	16.72	251	15	608	111.6	12.15	359	85	101	96.6	766	6	28	240	6.7
	26–31	0	14.79	221	13	538	98.6	6.24	204	67	106	57.7	782	5	31	288	7.2

* TN values in this patient include 37.4 and 45.3 g., respectively, of NPN.

1.0 meq./g. for each of these forms. All of these exchangers were more effective in this respect than the calcium cycle. With regard to potassium the hydrogen, ammonium and sodium forms proved to be equally effective in augmenting the loss of this electrolyte via the gastrointestinal tract. They were again superior to the calcium form. More potassium was excreted in the stool during potassium cycle resin administration than during the ingestion of any other form of the exchanger. It does not seem likely that this represents increased removal of endogenous or dietary potassium, since the amounts of this cation recovered in the stools were less than that administered in the resin. The large amount of potassium found in the stool would appear to be best explained by "unchanged resin" or the temporary release of potassium in the acid medium of the stomach and subsequent recovery of large amounts of the cation in the alkaline small intestine by the exchanger. The same reasoning regarding sodium may be applied to the sodium form of the carboxylic resin. Each gram of the potassium and sodium forms of the resin contained 3.8 meq. of their respective cations prior to administration.

E. Clinical concomitants of resin therapy

Ambulatory patients or those without discomfort tolerated the above cation exchangers quite well, whereas those with gastrointestinal symptoms or general malaise experienced varying degrees of difficulty in ingesting and retaining the larger

dosage. In some, emesis was extensive enough to prevent administration of the exchangers; these subjects have been excluded from our studies.

Seven of the studies with the hydrogen or ammonium forms of the resin were conducted in patients with diabetes mellitus. Though the carbohydrate data have been omitted for purposes of brevity the results indicated that the development of acidosis as a result of resin ingestion was not accompanied by ketone bodies in the urine and did not exert any visibly deleterious effect on car-

TABLE V

Statistical expression of urine data during H resin therapy

	Control and post resin*			Resin				
	Mean	No.	S. D.	Mean	No.	S. D.	"t"	"p"
Volume (*ml.*)	1026.1	20	531.2	1873.9 >†	22	775.9	3.99†	0.0025
Cl (*meq./d.*)	89.5	21	54.3	104.4	21	54.6	0.89	0.38
Na (*meq./d.*)	78.9	21	63.2	67.9	20	45.6	0.62	0.52
K (*meq./d.*)	39.5	21	23.1	35.8	21	19.2	0.55	0.62
TN (*g./d.*)	8.0	21	3.1	9.2	21	2.6	1.25	0.22

* Control and post resin periods combined after statistical demonstration that they were indistinguishable.
† Significantly greater than controls

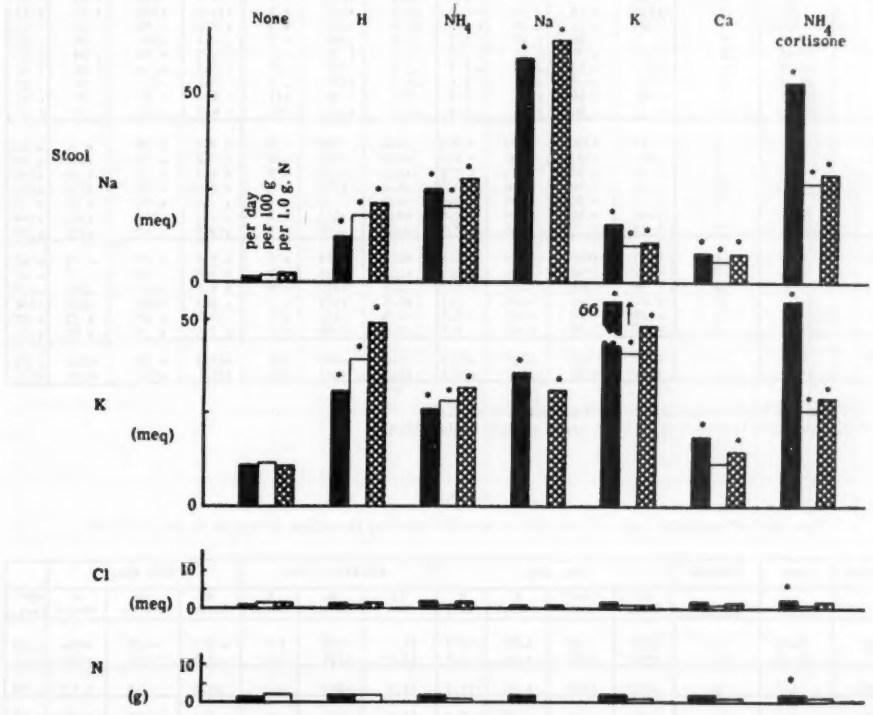

FIG. 2. STOOL DATA

The columns represent stool excretion of Na, K, Cl, and N per day, per 100 g. of wet stool, and per 1.0 g. of nitrogen during therapy indicated at the head of each group of columns. Again the chemical abbreviations indicate the form of the resin ingested, and the asterisks stand for values significantly different from the control column entitled "none." The column headed "NH_4 cortisone" indicates the patient receiving the NH_4 form of the resin together with cortisone. Stool excretion of sodium and of potassium increased to a variable degree irrespective of the particular form of the resin administered, or of cortisone therapy. Mean stool chloride and nitrogen values were not changed during the ingestion of any of the exchangers, but did increase slightly when cortisone was given during NH_4 form therapy in one patient.

TABLE VI

External, extracellular, and cell balances in subjects receiving the cation exchanger in the H cycle

Subject	Time	Therapy	Ext. Bal.				Extracell. Bal.			Cell Bal.			
	(Days)	(g./d.)	Cl (meq.)	Na (meq.)	K (meq.)	N (gm.)	H_2O (l.)	Na (meq.)	K (meq.)	N* (gm.)	Na (meq.)	K (meq.)	K** (meq.)
WW	0-3	0	+ 31	+ 31	- 21	+ 2.7	+0.5	+101	+ 4	+ 2.7	- 70	- 25	- 31
	3-6	0	+ 94	+ 59	+ 11	+ 6.0	+0.1	+ 29	- 4	+ 6.4	+ 30	+ 15	0
	6-9	25	+ 77	+ 30	- 92	+ 9.1	+0.6	+ 85	+ 2	+ 8.9	- 55	- 94	-115
	9-12	35	+ 25	+ 27	+ 7	+ 5.3	+0.3	+ 12	+ 5	+ 5.5	+ 15	+ 2	- 11
CAS	0-3	0	+ 62	+ 6	+ 55	+ 7.9	+0.6	+ 79	+ 5	+ 9.0	- 73	+ 50	+ 29
	3-6	0	+133	+148	+ 64	+10.2	+1.0	+182	- 4	+ 9.4	-134	+ 68	+ 46
	6-9	25	+175	+180	+ 81	+12.6	+1.1	+124	+20	+13.4	+ 56	+ 61	+ 29
	9-12	35	+ 55	+ 37	+107	+ 7.0	+0.3	+ 26	-12	+ 6.7	+ 11	+119	+103
VG	0-3	0	+ 28	- 7	+ 50	- 1.9	+0.1	+272	+ 9	- 4.7	-279	+ 41	+ 52
	3-6	0	+132	+ 66	+ 74	+10.3	+2.1	-116	- 5	+15.0	+182	+ 79	+ 43
	6-9	0	- 20	- 91	- 14	+ 0.4	+0.2	- 65	+ 1	+ 3.2	- 26	- 15	- 23
	9-12	32	- 1	- 46	- 28	- 0.1	-1.8	-366	- 2	- 0.1	+320	- 26	- 26
	12-15	32	- 17	+ 76	+ 13	- 0.6	-1.0	+ 36	-13	- 1.5	+ 40	+ 26	+ 30
	15-18	32	-303	- 19	+ 28	+ 6.7	-1.9	-318	-16	+ 6.7	+299	+ 44	+ 28
	18-21	0	-177	-107	+ 83	- 2.5	-0.3	+104	+ 9	- 9.8	-211	+ 74	+ 97
	21-24	0	- 68	- 46	+ 40	- 8.2	-0.1	- 80	+13	- 5.5	+ 34	+ 27	+ 40
	24-27	0	- 5	- 66	+ 46	- 2.1	+0.6	+117	-21	- 4.8	-183	+ 67	+ 78
WK	0-2	32	- 53	-100	+ 83	+ 8.3	-1.2	-198	- 8	+ 4.6	+ 98	+ 91	+ 80
	2-4	32	-105	-123	+ 90	+ 6.0	-0.9	-145	-12	+ 5.2	+ 22	+102	+ 90
	4-6	32	- 12	- 48	+133	+ 7.2	+0.1	+ 51	+ 5	+ 8.4	- 99	+128	+108
	6-8	32	- 20	- 44	+118	+ 0.9	-0.2	- 16	+ 3	+ 0.9	- 28	+115	+113
	8-9	32	+ 2	- 15	+ 83	+ 3.3	-0.3	- 41	- 6	+ 4.0	+ 26	+ 89	+ 79
	9-13	0	+ 22	- 48	+354	+ 2.6	+0.7	+113	+ 5	+ 2.2	-161	+349	+344
	13-15	0	+ 71	- 5	+204	+18.7	+0.6	+ 64	+ 9	+19.8	- 69	+195	+148
CBc	0-3	0	+105	+245	- 29	+ 5.1	+1.4	+147	+ 6	+ 5.4	+ 98	- 35	- 48
	3-6	0	+119	+152	- 23	+ 9.5	+1.1	+237	+ 2	+ 9.8	- 85	- 25	- 48
	6-9	32	- 90	-349	-254	+ 4.0	-1.2	-205	- 9	+ 4.7	-144	-245	-256
	9-12	32	+ 54	-149	-106	- 0.3	+0.6	+103	- 1	- 0.3	-252	-105	-104
	12-15	0	-139	-102	+ 44	+ 0.5	-0.8	-139	+ 7	- 0.1	+ 37	+ 37	+ 37
	15-19	0	- 87	- 86	+ 40	+ 7.5	-0.8	- 58	- 1	+ 7.5	+ 8	+ 41	+ 23
GDe	0-5	30	+ 31	-153	+136	+25.9	-1.3	-249	+15	+23.3	+ 96	+121	+ 65
	5-10	0	+108	+ 83	+195	+25.5	+1.3	+121	-11	+28.1	+206	+206	+139

* Value has been corrected for external balances of NPN
** K represents transfers of K in excess of protein metabolism

TABLE VII

External, extracellular, and cell balances in subjects receiving the cation exchanger in the NH_4 cycle

Subject	Time	Therapy	Ext. Bal.				Extracell. Bal.			Cell Bal.			
	(days)	(g./d.)	Cl (meq.)	Na (meq.)	K (meq.)	N (gm.)	H_2O (l.)	Na (meq.)	K (meq.)	N* (gm.)	Na (meq.)	K (meq.)	K** (meq.)
JF	6-12	0	+117	+ 59	+226	+12.1	+1.3	+195	+ 6	+ 9.0	-136	+220	+199
	12-18	40	+334	+342	+160	- 3.5	+1.8	+208	+22	- 2.2	+134	+138	+183
CBc	0-7	34	+279	+830	+ 31	-14.3	+1.9	+243	-12	-14.6	- 13	+ 43	+ 78
WT	0-6	40	+139	-128	+ 17	- 9.3	+1.0	+231	-15	- 6.9	-359	+ 32	+ 48
	6-12	0	- 36	+ 17	+ 76	-10.3	-0.3	-103	+ 7	- 6.6	+120	- 69	- 53
BT	4-10	0	-206	-217	+ 36	+ 0.5	-1.4	-201	+ 4	- 0.1	- 16	+ 32	+ 32
WD	0-5	0	-171	-269	+188	+18.4	-1.8	-206	- 6	+16.7	- 63	+194	+154
	5-10	0	- 24	- 52	+177	+13.9	+0.6	+100	+ 5	+15.5	-152	+172	+135
	10-15	0	- 51	- 13	+ 86	+ 7.9	-0.6	-110	0	+ 7.7	+ 97	+ 86	+ 68
	15-20	0	- 42	- 65	+126	+40.3	-0.7	- 84	-11	+40.5	- 19	+137	+ 41
	20-26	38	-117	-101	+267	+ 8.0	-1.0	-135	- 8	+ 7.6	+ 34	+275	+257
	26-31	0	+ 10	- 89	+144	+33.4	+0.3	+ 20	+ 3	+32.0	-109	+142	+ 66

* Value has been corrected for external balance of NPN
** K represents transfers of K in excess of protein metabolism

TABLE VIII

Body weight and analyses of blood and serum in subjects receiving the cation exchanger in the Na cycle

Subject	Time	Therapy	Body Wgt.	Blood		Serum							
(Age-Sex)	(Days)	(g./d.)	(kg.)	Sugar (mgms)	NPN (mgms)	HCO_3 (meq./l.)	Cl (meq./l.)	Na (meq./l.)	K (meq./l.)	Ca (mgms)	P (mgms)	H_2O (g./l.)	Protein (g.%)
EB	0	0	51.0	172	31	23.9	99.4	140	4.3	10.3	5.0	937	6.7
14 M	0-3	0	50.8	240	34	24.8	99.5	149	4.6	-	-	-	-
Diab.	3-6	0	51.0	273	33	25.4	100.8	144	5.3	9.8	5.0	-	7.2
	6-7	0	51.4	-	38	26.2	104.7	142	4.2	10.2	4.6	932	7.6
	7-10	40	51.8	226	33	27.0	101.0	138	4.3	-	-	-	-
	10-13	40	51.8	-	33	23.6	102.1	143	4.6	-	4.7	936	6.8
JV	0	0	54.2	173	32	25.7	96.7	139	3.8	10.2	3.8	932	6.5
15 M	0-3	0	54.4	318	36	25.4	97.7	147	4.5	-	-	-	-
Diab.	3-6	0	54.6	249	33	25.9	98.7	142	4.3	10.0	4.1	930	6.8
	6-7	0	54.0	-	35	26.3	98.7	-	5.3	10.2	4.6	-	7.0
	7-10	40	55.4	222	33	27.2	98.9	142	4.3	-	-	-	-
	10-13	40	55.4	-	34	25.3	99.1	143	4.8	-	4.0	928	6.7
VB	0	*	36.6	75	35	24.0	100.0	139	3.5	-	4.9	923	8.0
11 M	0-8	40	37.4	91	30	26.0	97.4	144	4.3	-	4.9	931	7.3
Rh. Fev.													

* End of Ca cycle resin

TABLE IX

Body weight and analyses of blood and serum in subjects receiving cation exchanger in the K cycle

Subject	Time	Therapy	Body Wgt.	Blood		Serum							
(Age-Sex)	(Days)	(g./d.)	(kg.)	Sugar (mgms)	NPN (mgms)	HCO_3 (meq./l.)	Cl (meq./l.)	Na (meq./l.)	K (meq./l.)	Ca (mgms)	P (mgms)	H_2O (g./l.)	Protein (g.%)
RC	0	0	48.4	-	31	24.4	97.0	150	5.2	10.0	3.8	-	-
13 M	0-4	60	47.4	-	37	22.7	100.7	140	4.2	-	-	934	-
Diabetes	4-6	60	47.2	311	35	25.1	99.7	142	4.2	10.0	4.4	936	7.0
	6-9	60	48.0	286	33	23.3	99.4	143	4.5	9.4	4.5	937	6.8
	9-12	60	48.8	288	33	25.0	101.0	148	4.6	9.1	4.1	931	-
EMc	0#	*	-	209	34	16.9	109.2	143	3.7	9.6	4.5	929	7.9
11 F	0-3	40	-	255	32	27.3	101.4	137	4.2	-	-	935	-
Diabetes													
CSt	0	0	60.2	-	31	27.6	101.7	145	4.4	8.9	2.1	938	-
54 M	0-6	40	-	-	34	28.7	100.5	145	6.1	8.8	2.9	936	6.7
Arthritis	6-12	0	-	-	35	26.0	106.1	147	4.0	9.2	2.7	930	7.0
WO	0**	**	30.0	-	37	26.6	105.0	141	3.8	-	-	-	-
12 M	0-5	0	29.8	-	44	26.6	101.5	137	4.0	10.0	4.6	925	7.8
Gl.Nephr.	5-10	40	29.8	-	40	28.1	99.6	145	4.4	10.1	5.5	-	8.1
(healed)													
CBc	0	0	47.5	-	39	28.9	86.7	137	4.3	8.8	4.1	-	6.6
33 F	0-5	32	48.7	-	38	29.4	90.8	142	6.1	8.8	5.0	939	6.3
C-V dis.													

* End of H cycle resin # Drawn on seventh day ** End of NH_4 cycle

TABLE X

Intake data and urine and stool output in subjects receiving the cation exchanger in the Na cycle

Subj.	Time	Therapy	Intake					Urine					Stool				
	(days)	(g./d.)	Fluid (l.)	Cl (meq.)	Na (meq.)	K (meq.)	N (gm.)	Vol. (l.)	Cl (meq.)	Na (meq.)	K (meq.)	TN (gm.)	Wgt. (gm)	Cl (meq.)	Na (meq.)	K (meq.)	N (gm)
EB	0-3	0	9.52	268	225	320	46.7	5.80	312	330	212	35.4					
	3-6	0	9.54	268	225	320	46.7	4.35	157	167	224	36.1	816	11	19	103	6.6
	6-7	0	3.23	89	75	107	15.6	1.70	64	49	81	13.1					
	7-10	40	9.97	282	681	337	49.1	4.32	169	332	130	33.1					
	10-13	40	9.52	279	678	333	48.6	5.55	264	-	-	42.7	-	1	466	236	4.9
JV	0-3	0	10.56	268	225	320	46.7	5.60	303	213	261	34.6					
	3-6	0	10.05	279	234	333	48.6	3.76	123	77	184	27.9	774	5	27	103	9.6
	6-7	0	3.23	89	75	107	15.6	1.51	74	54	83	11.0					
	7-10	40	9.83	272	672	325	47.4	2.99	84	344	144	27.0					
	10-13	40	9.71	274	674	327	47.7	4.61	-	-	-	32.0	-	4	192	74	2.9
VB	0-8	40	22.45	295	1201	716	123.5	16.70	233	411	180	106.2	2021	12	605	446	16.2

TABLE XI

Intake data and urine and stool output in subjects receiving cation exchanger in the K cycle

Subj.	Time	Therapy	Intake					Urine					Stool				
	(days)	(g./d.)	Fluid (l.)	Cl (meq.)	Na (meq.)	K (meq.)	N (gm.)	Vol. (l.)	Cl (meq.)	Na (meq.)	K (meq.)	TN (gm.)	Wgt. (gm.)	Cl (meq.)	Na (meq.)	K (meq.)	N (gm.)
RC	0-4	60	13.72	353	297	1334	95.1	12.70	440	318	492	-	1248	12	5	546	12.7
	4-6	60	6.96	183	154	675	49.2	5.25	204	236	157	45.2					
	6-9	60		Full	diab.	diet		7.72	473	563	742	46.6	745	3	27	299	8.7
	9-12	60		"	"			8.50	777	1020	450	-					
KDc	0-3	40		Full	diab.	diet		4.24	512	36	394	38.4	745	4	165	189	6.7
CBt	0-6	40		Full	diet			8.00	873	980	864	52.8	460	1	105	260	3.6
	6-12	0		"	"			6.40	705	752	284	41.6	386	3	28	108	4.6
WO	0-5	0	12.75	221	13	538	98.6	6.25	204	67	106	57.7	782	5	31	288	7.2
	5-10	40	12.52	227	14	552	101.2	5.75	227	71	504	46.3	799	6	10	133	8.7
CBc	0-5	32	11.26	225	189	877	39.2	2.45	0	7	515	33.0	1047	4	25	402	6.4

TABLE XII

External, extracellular, and cell balances in subjects receiving the cation exchanger in the Na cycle

Subject	Time	Therapy	Ext. Bal.				Extracell. Bal.			Cell Bal.			
	(Days)	(g./d.)	Cl (meq.)	Na (meq.)	K (meq.)	N (gm.)	H_2O (l.)	Na (meq.)	K (meq.)	N (gm.)	Na e (meq.)	K (meq.)	K** (meq.)
KB	0-3	0	- 51	-117	+ 64	+ 8.3	-0.5	+ 18	+ 1	+ 7.3	-135	+ 63	+46
	3-6	0	+104	+ 46	+ 52	+ 7.6	+0.8	+ 69	+10	+ 7.9	- 23	+ 42	+23
	6-7	0	+ 21	+ 20	+ 11	+ 1.0	-0.3	- 58	-12	- 0.7	+ 78	+ 23	+25
	7-10	40	+110	+112	+ 88	+13.2	+1.4	+153	+ 7	+14.9	- 41	+ 81	+45
	10-13	40	+ 12	-	-	+ 3.2	0	+ 59	+ 4	+ 3.2	-	-	-
JV	0-3	0	- 40	- 3	+ 15	+ 7.6	-0.5	+ 14	+ 5	+ 6.2	- 17	+ 10	- 5
	3-6	0	+151	+142	+105	+16.2	+1.2	+123	+ 3	+17.3	+ 19	+102	+61
	6-7	0	+ 12	+ 14	+ 9	+ 2.9	+0.1	+ 15	+12	+ 2.2	- 1	- 3	- 8
	7-10	40	+183	+114	+145	+18.6	+1.6	+234	- 5	+19.3	+ 80	+140	+94
VB	0-8	40	+ 48	+182	+ 89	+ 0.8	+0.7	+134	+ 9	+ 2.0	+ 48	+ 84	+75

* Corrected for balance of NPN
** Represents transfers of K in excess of the anabolism and catabolism of protein

TABLE XIII

External, extracellular, and cell balances in subjects receiving cation exchanger in the K cycle

Subject	Time	Therapy	Ext. Bal.				Extracell. Bal.			Cell Bal.			
	(days)	(g./d.)	Cl (meq.)	Na (meq.)	K (meq.)	N (gm.)	H_2O (l.)	Na (meq.)	K (meq.)	N* (gm.)	Na (meq.)	K (meq.)	K** (meq.)
RC	0-4	60	- 99	- 28	+478	-	-1.2	-270	-14	-	+242	+492	-
	4-6	60	- 27	- 87	+136	- 0.5	-0.1	0	- 1	+0.1	- 87	+137	+137
WO	0-5	0	+ 10	- 89	+144	+33.4	+0.3	+ 20	+ 2	+32.0	-109	+142	+ 66
	5-10	40	- 8	- 72	- 85	+45.9	+0.1	+ 68	+ 3	+46.7	-139	- 88	-199
CBc	0-5	32	+217	+152	- 40	- 0.8	+1.7	+288	+28	- 0.5	-136	- 68	- 67

* Value has been corrected for external balance of NPN
** Represents transfers of K in excess of protein metabolism

bohydrate metabolism. In view of the inherent variations in carbohydrate utilization from day to day, even in well-regulated diabetic patients, only this general statement is justified. The possibility of some influence of the acidosis, such as that described in dogs receiving ammonium chloride (4), cannot therefore be excluded.

Several of the studies were conducted in patients with edema. WK in Tables I, III, and VI is of particular interest in this respect because on a combination of marked sodium restriction and resin therapy his body weight dropped 5.6 kg. in nine days. The stool sodium excretion during this interval totaled 88 meq. It is obvious that this de-

TABLE XIV

Intake data and urine and stool output in subjects receiving the cation exchanger in the Ca cycle

Subj.	Time	Therapy	Intake					Urine						Stool				
	(days)	(g./d.)	Fluid (l.)	Cl (meq.)	Na (meq.)	K (meq.)	N (gm.)	Vol. (l.)	Cl (meq.)	Na (meq.)	K (meq.)	TN (gm.)	NPN (gm.)	Wgt. (gm)	Cl (meq.)	Na (meq.)	K (meq.)	N (gm.)
VB	0-2	0	4.77	74	4	179	21.2	1.71	44	-	-	13.5	-	1183	11	32	237	11.7
	2-8	40	15.14	221	13	537	92.6	11.20	242	110	226	90.5	-					
JF	0-5	0		Full	diab.	diet		8.25	480	1258	349	63.2	-	1457	6	61	153	9.0
	5-11	40		"	"	"		14.95	1809	1742	468	-	-					
	11-17	0	15.57	365	306	436	97.7	9.15	380	345	390	72.5	-	472	5	12	61	-
	17-23	40	26.69	709	595	847	123.6	11.50	430	309	421	97.3	-	647	6	8	99	5.5
CSt	0-6	0		Full	diet			7.40	936	907	335	45.1	-	291	2	105	83	2.0
	6-12	40		"	"			6.50	778	681	246	38.2	-	463	3	46	81	4.4
DY	0-6	50		("Salt-	free")	diet		12.50	421	413	249	59.5	53.5	1229	11	108	54	6.8
	6-11	60		"	"	"		10.40	219	201	251	55.6	44.8	1003	14	58	82	8.8
	11-16	60		"	"	"		11.00	0	117	298	54.8	47.6	961	7	46	94	9.0
HF	0-5	40		("Salt-	free")	diet		4.60	4	20	116	28.2	26.9	1049	11	56	121	7.7
	5-10	40		"	"	"		4.00	75	84	92	32.4	30.5	-	8	55	96	5.4
	10-16	33		"	"	"		4.80	140	115	93	40.3	35.5	1849	4	-	183	11.5

TABLE XV

Body weight and analyses of blood and serum in subjects receiving the cation exchanger in the Ca cycle

Subject	Time	Therapy	Body Wgt.	Blood		Serum							
(Age-Sex)	(Days)	(g./d.)	(kg.)	Sugar (mgm%)	NPN (mgm%)	HCO. (meq./l.)	Cl (meq./l.)	Na (meq./l.)	K (meq./l.)	Ca (mgm%)	P (mgm%)	H_2O (g./l.)	Protein (g.%)
VB	0	0	37.1	91	29	25.7	101.5	-	-	-	4.6	924	8.0
11 M	0-2	0	36.9	102	38	24.7	102.0	145	4.2	-	5.4	920	8.9
Rh.Fev.	2-8	40	36.6	75	35	24.0	100.0	139	3.5	-	4.9	923	8.0
JF	0*	*	68.5	45	39	28.3	101.2	146	5.1	10.1	4.0	927	-
29 M	0-5	0	69.5	98	41	26.9	98.6	145	5.3	9.9	3.0	925	7.3
Diab.	5-11	40	67.6	168	37	28.9	96.7	149	4.8	-	-	928	7.0
	11-17	0	67.6	37	32	29.3	96.8	140	3.4	10.9	3.9	926	6.8
	17-23	40	67.6	-	37	27.8	93.6	134	3.3	9.9	-	928	7.2
CSt	0**	**	-	-	32	26.3	104.9	143	5.0	9.3	3.2	934	6.8
54 M	0-6	0	-	105	30	27.2	102.0	143	4.5	9.2	2.7	931	6.9
Arthr.	6-12	40	-	77	28	27.2	100.3	144	3.9	9.2	3.4	937	6.5
DY	0*	*	-	89	45	17.3	108.0	135	3.9	7.8	4.5	921	4.3
12 M	0-6	50	28.4	-	39	21.5	104.6	136	4.1	8.2	4.5	925	4.3
Nephro.	6-11	60	29.6	-	38	21.3	104.1	143	4.1	8.4	4.8	933	3.8
	11-16	60	30.6	-	38	23.1	101.7	141	3.9	7.6	4.6	929	3.8
HF	0*	*	21.0	-	28	24.1	102.3	139	3.8	8.6	5.3	-	3.9
5 M	0-5	40	-	-	36	22.6	99.8	135	4.1	7.5	5.7	928	3.7
Nephro.	5-10	40	-	-	32	20.9	103.7	138	4.4	-	-	935	4.0
	10-16	33	-	87	31	20.7	102.7	134	4.0	-	5.0	935	3.9

* End of H and K resin period

** End of NH_4 and K resin period

TABLE XVI

External, extracellular, and cell balances in subjects receiving the cation exchanger in the Ca cycle

Subject	Time	Therapy	Ext. Bal.				Extracell. Bal.			Cell Bal.			
	(Days)	(g./d.)	Cl (meq.)	Na (meq.)	K (meq.)	N (gm.)	H_2O (l.)	Na (meq.)	K (meq.)	N* (gm.)	Na (meq.)	K (meq.)	K** (meq.)
VB	0-2	0	+ 24	-	-	+ 4.5	-	-	-	-	-	-	-
	2-8	40	- 31	-124	+133	- 7.0	-0.1	- 69	- 6	- 6.3	- 55	+139	+154
JF	11-17	0	- 22	- 55	- 15	-	-0.2	-150	-21	-	+ 95	+ 6	-
	17-23	40	+271	+274	+327	+20.5	+3.0	+327	+ 7	+16.3	+181	+320	+276

* Value has been corrected for external balance of NPN

** Represents transfers of K in excess of protein metabolism

crease in endogenous sodium as a result of stool losses could not by itself account for the extensive decrease of edema. The bulk of the sodium was lost in urine. It seems probable that the additive effect of the acidosis should be listed among other factors contributory to this diuresis.

On the other hand in patient CSc in the same tables much larger amounts of sodium were excreted in stools during the administration of the exchanger together with a milk diet unrestricted as to sodium. It is reasonable to suggest that without resin to interfere with the absorption of the ingested sodium this patient would not have lost edema fluid. Patient GDe demonstrates the degree to which the efficacy of the resin in augmenting stool sodium can vary not only from patient to patient, but also in the same subject. In the 10 to 15 day period he lost much less sodium per day in stool than in the somewhat longer 19 to 25 day interval. In this patient it is again worth pointing out that his initial huge diuresis with a body weight loss of 9.9 kg. cannot be attributed to stool losses of sodium, but that the marked acidosis which appeared during resin therapy may have hastened the delivery of the edema fluid.

Finally it should be pointed out that these exchangers have been administered to patients with renal failure. These can be most readily identified by the elevated blood nonprotein nitrogen values in the various tables of serum and blood data. The fact that in this series no complications developed such as clinical acidosis or potassium intoxication does not mean that these exchangers can be used with impunity in all forms of renal disease. The risks and benefits have been described in greater detail in another paper in this series (5). Insofar as the current studies are concerned it should be emphasized that they were of limited duration and interrupted short of undesirable or dangerous changes when certain trends had become well established, as with the acidosis in GDe, Table I. Incidentally, the ammonium released from the ammonium form of the resin apparently does not raise whole blood nonprotein nitrogen, but it may have, in some patients, as in WG, Table IV, raised the output of nitrogen in urine.

DISCUSSION

The data which have been presented indicate that the hydrogen and the ammonium forms of the resin produce effects which are indistinguishable, including essentially equal tendencies to induce acidosis and to increase the excretion of sodium and potassium in the stool. Furthermore, neither influences the output of nitrogen and chloride via this route. Although the efficiency of these resins is relatively low *in vivo*, it is clear that they may be useful in reducing the absorption of sodium from the diet so that a patient requiring low sodium therapy could ingest food seasoned with more of this cation. That he could not ingest much larger amounts of salt should be clear from the data indicating that each gram of the hydrogen or ammonium forms will remove only up to 1 meq. of sodium.

These studies also support an interpretation voiced elsewhere (1), *i.e.*, that the acidifying resins produce certain serum effects similar to those which follow the use of diuretics such as ammonium chloride, potassium nitrate, et cetera. This suggests that the diuresis accompanying hydrogen or ammonium cycle resin therapy of patients cannot be augmented by the use of acidifying diuretics. On the other hand it is reasonable to predict that mercurial diuretics used in conjunction with these two acidifying resins will exert their maximal effects without the aid of ammonium chloride. There is, however, probably an increased danger of producing potassium depletion under these circumstances which may be counteracted by administration of extra potassium.

Certain extrapolations seem justified with respect to possible clinical application of the sodium and potassium cycle resin findings. The relatively high efficiency of the sodium cycle resin in augmenting the stool output of potassium suggests its possible application in renal insufficiency of the salt-wastage and potassium accumulation type. This agent under such circumstances should augment the external losses of potassium and simultaneously cancel the negative balances of sodium which characterize this disorder (6–8).

The effects of the potassium cycle exchanger suggest that it may be beneficially employed in combination with the hydrogen or ammonium cycle congeners. It is obvious that upon exchange with sodium and hydrogen present in the intestinal tract the released potassium becomes available for absorption and is, as the data indicate, in great measure retained. This effect should serve to cancel

the deficits of potassium accompanying prolonged use of the hydrogen or ammonium cycle resins without adding to their acidifying effects; although the same purpose may more efficiently be served by increasing dietary potassium intake by means of a salt such as $KHCO_3$ or KCl. The clinical practicality of such combinations has been evaluated elsewhere (9). In addition, the danger of producing potassium intoxication in patients with oliguria and renal disease must be recognized (10–12).

It is possible that certain features of these resins may be utilized in cancelling some of the side effects of prolonged cortisone or ACTH therapy such as alkalosis, sodium retention, and potassium depletion (13–16). For example, combinations of hydrogen and potassium exchangers may be effective in this regard. Potassium depletion, however, may be enhanced under these circumstances unless the intake of potassium is large enough to counteract the combined effects of the resin and ACTH or cortisone on this ion. This problem has been studied in some detail in a subsequent paper (17).

Finally, the lack of any marked effects upon ingestion of the calcium cycle resin is both a disappointment and a reassurance. From the theoretical point of view the resin in this cycle should be useful in far-advanced renal insufficiency: release of the calcium ion from the exchanger should *a*) increase stool losses of sodium and of potassium which accumulate in kidney failure, and *b*) provide calcium to accelerate phosphate losses as insoluble salts via the bowel and alternatively replace the deficits characteristically present in serum and extracellular fluid of such patients. Unfortunately, neither of these predictions is substantiated by our data. These studies, however, provide a highly satisfactory control for a number of the other reports in this series. The following conclusion is inescapable, if such support be needed: the effects of the ammonium, hydrogen, sodium, and potassium forms of the carboxylic cation exchanger under investigation in this series of studies are attributable to the attached cation and not to the resin itself. If the cation with which the resin is charged is not displaced in sufficient quantity the resin has no detectable effect.

SUMMARY

1. The ammonium cycle resin produces effects quite comparable to those seen with hydrogen cycle resin ingestion, *i.e.*, hyperchloremia develops, and serum carbon dioxide content falls while the stool sodium and potassium excretion rises.

2. The stool changes seen with either the ammonium or the hydrogen cycle resins are also observed in subjects receiving the exchanger in either the potassium or sodium cycle. In the use of the latter the efficiency in removing potassium is less. Neither consistently affects the serum constituents but occasionally hyperkaliemia appears during potassium resin therapy. With the sodium form of the resin, sodium balances become positive with extracellular retention of this cation. With potassium resin, the intracellular stores of potassium may rise during therapy.

3. In a series of studies on one patient concomitant administration of cortisone did not interfere with the ability of the ammonium resin to raise stool sodium and potassium but hypokaliemia appeared.

4. The calcium cycle of the carboxylic cation exchanger in the form used was relatively inert and produced much smaller changes in stool sodium and potassium. These findings, however, do add support to the view that the cycle of the resin and not the resin *per se* is the determinative factor in the observed results.

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ACIDIFYING AND NON-ACIDIFYING CARBOXYLIC RESIN MIXTURES USED ALONE AND WITH ACTH OR CORTISONE

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Evidence has been presented indicating that a sufficient intake of a carboxylic cation exchanger in the potassium cycle increases the stool output of sodium in absolute as well as in relative terms (1–4). Two other findings accompanying the use of this form of the resin are noteworthy: *a*) a significant proportion of the potassium taken with or as part of the resin can be retained in the body and *b*) ingestion of this particular resin does not produce acidosis. Its efficiency in removing sodium is probably not as great, however, as that of either the hydrogen or the ammonium forms of the resin, each of which interferes with potassium absorption and induces a metabolic acidosis. The first half of this paper deals with findings observed during the simultaneous administration of the two types of resin in equal proportions, *i.e.*, potassium cycle mixed with either the hydrogen or the ammonium cycle, as well as in mixtures in which the acidifying resin predominated.

The second half of this report describes results obtained during the use of resin mixtures with ACTH or cortisone or both. The expanding recourse to adrenal cortical effects in the therapy of a wide variety of disease states (5–7) has further emphasized that prolonged therapy is frequently not possible because of two particularly undesirable concomitants, *i.e.*, sodium retention and potassium depletion. It seems probable that these side effects by necessitating interruption or intermittency of treatment deprive patients of benefits which might be otherwise obtainable. The combined resin and steroid or hormone studies herein presented describe attempts at prevention or deferment of such deviations in cation metabolism.

MATERIALS AND METHODS

Equal parts of the acidifying and non-acidifying exchange resins were administered in capsules for a daily total of 24 to 60 g. to hospitalized children or adults during 16 periods three to seven days in lengtl.. Mixtures preponderating in the acidifying resin, *i.e.*, 75 to 80% in the ammonium or hydrogen cycle, were given in eight subsequent studies in four patients. In the final group of experiments four parts of ammonium or hydrogen form resin and one part of the potassium resin were administered to patients undergoing treatment with adrenocorticotrophic hormone or cortisone. In all three groups of studies control periods were included when possible. The experimental procedures and other pertinent information have been described earlier (1, 2). The dietary regimens employed, the results of blood and serum analyses, and the available balance data are presented in tabular form. To assist interpretation the findings have been expressed statistically wherever possible and presented in graphic form.

RESULTS

A. Relative constancy of serum and blood values during administration of resins in mixtures of equal proportion

Concentrations of the various serum constituents recorded in Table I at the end of the administration of equal amounts of the hydrogen and potassium cycle resins have been compared, irrespective of the dietary regimen, with the levels present prior to this treatment and expressed as increments or decrements, prefaced by the appropriate signs. The averages of these changes are depicted in Figure 1. It is readily evident that only slight fluctuations occurred in serum bicarbonate, chloride, sodium, potassium, calcium, phosphorus, protein, and water. Statistical comparison of the changes recorded during hydrogen-potassium resin ingestion, by means of the "t" test with a larger group of control periods described in a precedir.g paper, indicates that they are indistinguishable in magnitude and direction. It is clear, therefore, that in these subjects there is no evidence of the hyperchloremia and metabolic acidosis which characteristically occurred during hydrogen cycle resin therapy of equal duration (1). It should be em-

TABLE I

Body weight and analyses of blood and serum in subjects receiving equal parts of the H and the K cycle resin

Subject	Time	Therapy (g./d.)		Body Wgt.	Blood		Serum							
(Age-Sex)	(Days)	H	K	(kg.)	Sugar (mgm%)	NPN (mgm%)	HCO_3 (meq./l.)	Cl (meq./l.)	Na (meq./l.)	K (meq./l.)	Ca (mgm%)	P (mgm%)	H_2O (g./l.)	Protein (g.%)
DL	0	0	0	50.6	350	36	23.1	98.8	143	5.6	10.2	3.7	-	8.1
14 F	0-3	16	16	49.8	-	38	21.2	95.0	141	4.4	-	-	909	7.5
Diabetes	3-6	16	16	50.4	136	34	27.2	100.0	144	4.4	9.8	4.6	923	6.6
	6-9	20	20	51.2	229	34	23.9	100.5	143	5.1	9.9	3.8	925	7.4
	9-11	30	30	51.0	-	35	26.3	98.3	147	4.4	10.4	4.6	-	8.1
JF	0	0	0	68.9	69	32	28.1	104.0	147	5.0	9.5	4.4	934	7.3
29 M	0-6	20	20	68.5	45	39	28.3	101.2	146	5.1	10.1	4.0	927	-
Diabetes	6-11	0	0	69.5	98	41	26.9	98.6	145	5.3	9.9	3.0	925	7.3
DI	0*	*	*	30.2	-	34	20.4	113.6	148	3.5	7.9	4.4	-	4.7
12 M	0-6	17	17	30.4	67	44	23.1	108.6	141	3.7	6.7	5.0	936	3.7
Nephrosis	10	0	0	31.4	-	33	19.0	113.7	140	3.1	-	4.2	938	3.5
	10-16	0	0	31.4	-	36	20.5	110.1	139	4.0	7.3	4.5	933	3.6
	16-22	20	20	[	-	31	20.7	108.4	137	3.8	7.5	4.6	931	4.1
	22-28	12	12	[	-	41	19.2	109.7	145	3.9	7.3	4.9	927	-
	28-35	20	20	31.4	91	40	20.6	109.7	144	5.1	7.4	4.3	930	3.8
	42*	*	*	30.8	-	48	16.2	106.7	143	3.5	6.4	6.9	943	3.1
	42-46	0	0	28.4	-	47	19.8	104.1	145	3.2	7.2	5.4	926	3.9
	46-52	33	33	-	89	45	17.3	108.0	135	3.9	7.8	4.5	921	4.3
	68	0	0	30.6	-	38	23.1	101.7	141	3.9	7.6	4.6	929	3.8
	68-73	30	30	31.8	-	41	23.7	111.2	-	4.4	7.3	4.3	929	3.6
	73-80	21	21	32.0	-	46	21.6	111.1	142	4.6	7.5	-	-	3.4
EF	0	0	0	17.9	76	53	25.3	102.1	140	5.2	8.3	4.6	933	4.4
6 M	0-7	20	20	21.4	-	33	21.9	102.7	141	4.2	8.2	4.8	935	4.0
Nephrosis	7-14	20	20	21.5	-	29	22.8	100.4	143	4.2	8.0	5.0	932	3.9
	14-21	20	20	20.8	-	28	24.1	102.3	139	3.8	8.6	5.3	-	3.9
	37	0	0	20.8	87	31	20.7	102.7	134	4.0	-	5.0	935	3.9
	37-44	25	25	20.2	-	32	23.6	100.0	135	3.4	-	6.2	-	3.9

* End of H resin

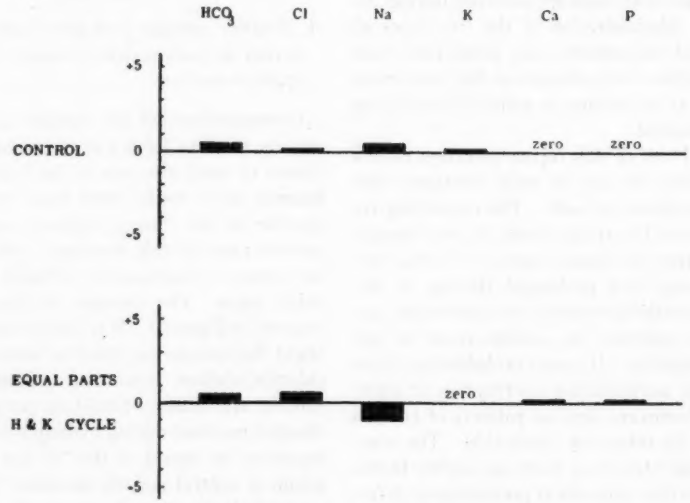

FIG. 1. FLUCTUATIONS IN SERUM CONSTITUENTS

The columns represent mean changes in serum HCO_3, Cl, Na, and K in milliequivalents per liter and in serum Ca and inorganic P in milligrams % between the onset and end of control periods and of periods in which equal parts of H and K cycle resins were ingested in amounts indicated in Table I. There were no significant changes from the control values during ingestion of the resin mixture.

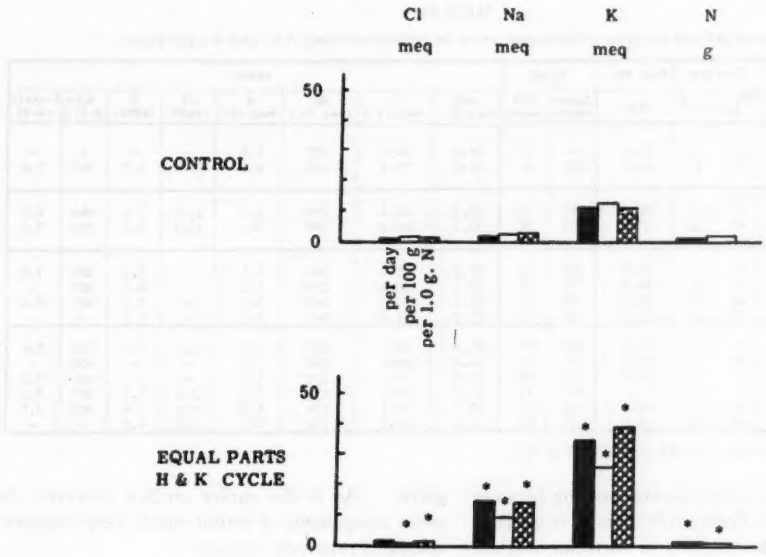

FIG. 2. STOOL DATA

The columns indicate the mean excretion of Cl, Na, K, and N per day, per 100 g. of wet stool, and per 1.0 g. of stool nitrogen during control and resin mixture regimens. The asterisks signify statistically significant increases ("p" for the "t" test equals 0.05 or less) in stool excretion of all substances represented during ingestion of the resin mixture. The changes in chloride and of nitrogen are small, however.

phasized, however, that in these experiments the average intake of the hydrogen cycle cation exchanger was approximately one-half of that in the studies cited above.

Similarly, though the data are limited in number, it can be seen by inspection that the resin mixtures did not produce any definite trend in the blood sugar and nonprotein nitrogen values, and that using the ammonium rather than the hydrogen cycle resin in the mixture with the potassium cycle exchanger does not detectably alter the relative constancy of the serum or blood constituents under scrutiny (Tables I and II).

B. Acidosis and hyperchloremia observed in patients given 80: 20 mixtures of acidifying and non-acidifying resins

All of the patients receiving the exchangers in the above proportions developed some measure of acidosis. This was usually associated with a proportionate increase in the serum chloride. Serum sodium, potassium, calcium, phosphorus, and protein fluctuated about the pretreatment values. If the latter were within the normal range initially, and this was true in all but patient JL, the changes during therapy were not of sufficient magnitude to reach levels which were abnormally high or low (Table II).

C. Serum and blood constituents in patients given resin mixtures in the course of ACTH or cortisone therapy

From Table III it is evident that during the simultaneous administration of ACTH or cortisone and resin mixtures the serum concentrations of bicarbonate and of chloride still decreased and increased, respectively. The findings in this limited number of observations suggest that the magnitude of the changes was somewhat less than those described earlier with the resin mixtures alone. All

TABLE II

Body weight and analyses of blood and serum in subjects receiving NH_4 and K cycle resins

Subject	Time	Therapy		Body Wgt.	Blood		Serum							
(Age-Sex)	(days)	NH_4 (g./d.)	K	(kg.)	Sugar (mgm%)	NPN (mgm%)	HCO_3 (meq./l.)	Cl (meq./l.)	Na (meq./l.)	K (meq./l.)	Ca (mgm%)	P (mgm%)	H_2O* (g./l.)	Protein (g.%)
RT	0	0	0	45.0	-	28	27.2	92.6	137	4.8	-	-	-	-
5 F	0-6	45	15	43.8	257	38	22.6	97.3	136	4.1	10.6	5.7	928	7.6
Diabetes														
RS	0	0	0	38.0	66	35	25.9	100.1	139	4.0	10.6	6.0	940	6.1
11 M	0-5	48	12	37.2	125	28	18.1	104.2	140	4.5	10.3	6.0	932	7.1
Diabetes														
FC	0	0	0	47.2	100	24	23.9	97.0	141	4.5	-	5.5	927	7.8
13 M	0-7	48	12	44.3	79	29	18.3	100.2	139	4.1	-	6.0	927	-
Rh.fever	7-14	48	12	48.0	78	23	25.1	100.5	145	4.0	-	5.1	925	8.0
	14-21	48	12	49.1	85	21	23.5	102.8	140	4.0	-	5.3	-	-
JL	0	0	0	37.0	359	49	21.0	97.0	132	5.8	10.3	5.0	930	7.4
14 M	0-3	48	12	36.0	153	66	14.2	104.0	148	5.6	-	-	930	-
Gl.neph.	0	0	0	37.2	339	60	22.9	97.1	137	5.8	-	-	931	7.2
Diabetes	0-5	0	0	-	265	41	27.7	90.9	136	5.9	11.8	5.1	925	8.1
	5-14	48	12	37.0	352	42	17.4	99.1	134	4.7	10.5	5.4	929	7.5
	14-21	48	12	36.0	348	48	14.2	107.6	132	4.5	9.7	4.2	-	-

* Calculated as $W_s = 0.985 - (0.00745 \times P_s)$

subjects developed hypokaliemia ranging between 3.4 and 3.1 meq./l. during this therapy in contrast to the findings when ACTH or cortisone was not given. As in the earlier studies, however, the other components of serum which were measured remained relatively constant.

TABLE III

Body weight and analyses of blood and serum in subjects receiving NH_4 and K cycle resins together with ACTH or cortisone

Subject (Age-Sex)	Time (Days)	Therapy			Body Wgt.	Blood		Serum							
		Resin		ACTH											
		NH_4 (g./d.)	K	(mgm./d.)	(kg.)	Sugar (mgm. %)	NPN (mgm. %)	HCO_3 (meq./l.)	Cl (meq./l.)	Na (meq./l.)	K (meq./l.)	Ca (mgm. %)	P (mgm. %)	H_2O* (g./l.)	Protein (g. %)
BS	0	0	0	0	52.7	82	30	26.7	99.5	141	4.0	10.4	4.0	931	7.2
37 F	0–5	48	12	300	50.0	47	30	17.3	100.5	139	3.4	10.1	4.4	928	7.7
Sclero-derma	5–11	0	0	300	49.8	114	43	26.1	99.4	135	4.3	9.5	4.0	937	6.4
BM	0	0	0	0	41.3	80	37	25.5	97.5	138	4.5	—	5.2	920	8.7
14 F	0–7	48	12	100	41.1	79	34	23.1	101.1	142	3.4	—	4.7	933	7.0
Rh. fever	7–14	48	12	100	44.0	98	30	24.7	103.1	137	4.0	—	5.0	—	—
	14–21	48	12	100	45.9	91	32	21.1	103.1	140	3.8	—	5.1	—	—
BC	0	0	0	0	40.2	80	39	21.8	109.4	136	3.6	6.0	5.5	—	—
12 M	0–7	48	0†	100	37.8	100	69	11.8	120.8	138	3.2	6.6	5.4	—	—
Nephrosis															
RL	0	0	0	200‡	57.3	80	36	29.5	99.2	139	4.4	—	—	937	6.5
42 M	0–7	48	12	200‡	57.7	—	46	29.5	98.0	144	3.2	—	—	937	6.4
Hemolytic anemia	7–13	48	12	200‡	57.7	77	33	27.5	95.3	137	4.1	9.5	4.6	932	7.1
JM	0	0	0	300	80.0	75	32	30.2	99.8	140	3.8	8.4	4.0	945	5.4
20 M	0–7	48§	12	300	—	97	36	25.2	97.2	143	3.1	—	4.2	—	—
Aplastic anemia															

* Calculated as $W_s = 0.985 - (0.00745)(P_s)$
† Ingested 50 meq. $KHCO_3$/day instead of K cycle resin
‡ Oral cortisone instead of ACTH
§ H cycle resin administered instead of NH_4 cycle

TABLE IV

Intake data and urine and stool output in subjects receiving equal parts of the H and the K cycle resin

Subj.	Time (Days)	Therapy		Intake					Urine						Stool				
		H (g./d.)	K (g./d.)	Fluid (l.)	Cl (meq.)	Na (meq.)	K (meq.)	N (g.)	Vol. (l.)	Cl (meq.)	Na (meq.)	K (meq.)	TN (g.)	NPN (g.)	Wgt. (g.)	Cl (meq.)	Na (meq.)	K (meq.)	N (g.)
DL	0–6	16	16	20.74	506	424	1070	88.1	—	—	—	—	—	—	720	7	54	144	3.3
	6–9	20	20	9.99	250	210	523	43.5	7.30	135	7	353	37.3	—	66	1	14	50	0.7
	9–11	30	30	7.30	167	140	424	29.0	4.95	152	52	260	22.8	—					
JF	0–6	20	20	Full diab. diet					11.50	1799	1371	740	91.7	—	1073	2	36	203	6.2
	6–11	0	0						8.52	480	1258	349	63.2	—	—	—	—	—	—
DY	0–6	17	17	Full diet					10.70	840	792	654	73.2	61.4	838	2	60	193	8.4
	10–16	0	0	11.03	146	9	354	65.0	7.05	338	197	270	58.0	45.3	1171	11	26	48	6.3
	16–22	20	20	13.67	192	11	467	83.7	6.70	328	114	279	55.7	46.1	983	11	35	167	9.6
	22–28	12	12	13.67	180	11	438	80.4	9.60	343	216	468	67.5	54.0	981	12	43	124	9.2
	28–35	20	20	17.29	192	11	466	85.5	8.48	309	119	108	73.9	63.1	758	7	33	149	9.7
	42–46	0	0	8.10	64	4	156	28.6	8.10	427	383	198	42.8	33.8	677	1	23	13	3.4
	46–52	33	33	"Salt-free" diet					14.20	340	213	454	71.1	60.1	981	—	158	241	7.6
	68–73	30	30						11.00	0	23	403	48.6	38.7	1061	5	93	271	9.5
	73–80	21	21						14.10	194	150	661	84.9	69.8	2007	13	58	125	13.1
BF	0–7	20	20	Full diet					5.38	177	9	288	39.4	36.5	—	14	318	614	18.8
	7–14	20	20	"Salt-free" diet					6.45	259	58	505	36.6	34.2					
	14–21	20	20						5.75	170	23	281	31.5	29.3	881	3	—	333	7.2
	37–44	25	25						7.00	124	50	383	40.2	35.8	1310	4	149	690	9.1

D. Stool composition during ingestion of cation exchange resins in two different cycles (Table IV)

As in all of the earlier studies with the individual resins (1) there is no evidence that these several forms of the resin in combination alter the output of either chloride or of nitrogen per day, per unit of stool mass, or per unit of stool nitrogen. The second line of Figure 2 expresses mathematically the stool data in Table IV in the 14 periods in which the subjects received the resins in equal proportions while on a full or a so-called hospital "salt-free" diet. The exclusion of the three periods in which patient DY was maintained on a regimen markedly restricted as to sodium permits comparison of data derived from dietetically homogeneous groups. This is necessary because of the demonstration that maintenance on a no-salt milk formula of the type which subject DY received in itself alters stool composition (8). The control material (Figure 2, line 1) repeated from an earlier paper, represents therefore the average content of chloride, sodium, potassium, and nitrogen to be expected in the stools of individuals receiving a substantial amount of sodium, whether it be in milk or in a diet that is or is not labelled "salt-free." It is readily evident that the hydrogen-potassium resin

TABLE V

Intake data and urine and stool output in subjects receiving NH_4 and K cycle resins

Subj.	Time (Days)	Therapy		Intake					Urine					Stool				
		NH_4 (g./d.)	K (g./d.)	Fluid (l.)	Cl (meq.)	Na (meq.)	K (meq.)	N (g.)	Vol. (l.)	Cl (meq.)	Na (meq.)	K (meq.)	TN (g.)	Wgt. (g.)	Cl (meq.)	Na (meq.)	K (meq.)	N (g.)
RT	0–6	45	15	21.32	363	306	773	96.4	13.72	383	64	329	101.5	1058	6	358	620	4.6
RS	0–5	48	12	22.04	434	364	743	114.8	12.28	304	95	230	79.8	294	9	27	168	3.0
FC	0–7	48	12	19.94	415	348	815	109.8	10.63	503	159	269	81.8	1471	14	99	520	9.1
	7–14	48	12	Full diet					7.30	856	269	166	67.4	1006	8	343	273	8.0
	14–21	48	12						5.95	703		209	50.3	1437	10	295	415	10.9
JL	0–3	48	12	12.52	260	218	446	68.9	7.80	233	131	264	54.6	110	1	71	78	0.6
	0–5	0	0	"Salt-free" diet					1.40	26	18	49	8.0	623	2	2	37	4.4
	5–14	48	12						15.40	145	148	476	117.0	1230	2	14	198	8.4
	14–21	48	12						14.50	146	72	186	101.5	1547	14		593	12.2

mixture taken in equal amounts raises the stool output of potassium in absolute values to a greater degree than stool sodium.

On the other hand, examination of the intake and excretion data in the children and adults given the resin mixtures which contained predominantly hydrogen or ammonium form resins (Table V), clearly indicates that the stool sodium and potassium values exceeded by a statistically significant margin the mean output of these ele-

TABLE VI

Intake data and urine and stool output in subjects receiving NH_4 and K cycle resins together with ACTH or cortisone

Subj.	Time (*Days*)	Therapy: Resin NH_4 (*g./d.*)	Therapy: Resin K (*g./d.*)	Therapy: ACTH (*mgm./d.*)	Intake: Fluid (*l.*)	Intake: Cl (*meq.*)	Intake: Na (*meq.*)	Intake: K (*meq.*)	Intake: N (*g.*)	Urine: Vol. (*l.*)	Urine: Cl (*meq.*)	Urine: Na (*meq.*)	Urine: K (*meq.*)	Urine: TN (*g.*)	Stool: Wgt. (*g.*)	Stool: Cl (*meq.*)	Stool: Na (*meq.*)	Stool: K (*meq.*)	Stool: N (*g.*)
BS	0–5	48	12	300	12.06	119	7	518	52.9	10.25	303	102	287	88.2	700	3	181	373	5.2
	5–11	0	0	300	10.73	113	7	272	50.0	6.20	90	26	68	83.1	338	2	57	235	2.3
BM	0–7	48	12	100	16.54	411	345	806	108.7	10.36	383	210	264	87.0	1592	34	259	504	12.2
	7–14	48	12	100	Full diet					6.20	872	685	222	77.1					
	14–21	48	12	100						8.93	1100	893	232	80.4	1577	17	251	512	12.3
BC	0–7	48	0*	100	"Salt-free" diet					—	—	—	—	—	853	2	374	358	6.7
RL	0–7	48	12	200†	"Salt-free" diet					—	—	—	—	—	1284	6	101	556	13.8
	7–13	48	12	200†						17.20	918	705	471	72.2	2434	23	376	724	20.9
JM	0–7	48‡	12	300	16.35	294	261	553	73.7	8.70	393	177	244	136.6	1515	2	299	538	5.3

* 50 meq. $KHCO_3$ ingested per day
† Oral cortisone
‡ Received H cycle resin instead of NH_4

TABLE VII

External, extracellular, and cell balances in subjects receiving equal parts of the H and the K cycle resin

Subject	Time (Days)	Therapy: H (g./d.)	Therapy: K (g./d.)	Ext. Bal.: Cl (meq.)	Ext. Bal.: Na (meq.)	Ext. Bal.: K (meq.)	Ext. Bal.: N (gm.)	Extracell. Bal.: H_2O (l.)	Extracell. Bal.: Na (meq.)	Extracell. Bal.: K (meq.)	Cell Bal.: N* (gm.)	Cell Bal.: Na (meq.)	Cell Bal.: K (meq.)	K** (meq.)
DL	6–9	20	20	+112	+193	+150	+5.5	+0.9	+119	+11	+ 5.5	+74	+139	+126
	9–11	30	30	+ 11	+ 79	+134	+5.6	+0.4	+102	- 6	+ 5.3	-23	+140	+127
DY	10–16	0	0	-206	-217	+ 36	+0.5	-1.4#	-201	+ 4	- 0.1	-16	+ 32	+ 32
	16–22	20	20	-149	-141	+ 21	+18.2	-1.1	-167	- 6	+19.2	+26	+ 27	- 19
	22–28	12	12	-177	-252	-154	+3.7	-1.5	-165	- 5	+ 1.7	-87	-149	-153
	28–35	20	20	-127	-144	+209	+1.7	-1.0#	-161	+ 6	+ 1.9	+17	+203	+199
	42–46	0	0	-367	-406	- 55	-17.8	-3.1	-408	-12	-17.6	+ 2	- 43	- 1

* Balances of N in excess of transfers of NPN
** Value corrected for anabolism or catabolism of protein
\# In view of persistent edema, chloride space in this patient was taken to equal 30% of body weight

TABLE VIII

External, extracellular, and cell balances in subjects receiving NH_4 and K cycle resins

Subject	Time (*Days*)	Therapy: NH_4 (*g./d.*)	Therapy: K (*g./d.*)	External bal.: Cl (*meq.*)	External bal.: Na (*meq.*)	External bal.: K (*meq.*)	External bal.: N (*g.*)	Extracell. bal.: H_2O (*l.*)	Extracell. bal.: Na (*meq.*)	Extracell. bal.: K (*meq.*)	Cell. bal.: N* (*g.*)	Cell. bal.: Na (*meq.*)	Cell. bal.: K (*meq.*)	Cell. bal.: K† (*meq.*)
RT	0–6	45	15	− 27	−120	−176	−10.0	−0.7	−100	−8	−12.8	− 20	−168	−138
RS	0–5	48	12	+118	+238	+345	+31.7	+0.6	+103	+7	+33.4	+135	+338	+258
FC	0–7	48	12	−105	+ 86	+ 26	+18.6	−1.2	−189	−8	+17.2	+275	+ 34	− 7
JL	0–3	48	12	+ 24	+ 12	+104	+13.4	−0.3	+ 79	−3	+ 9.4	− 67	+107	+ 85

* Balance of N in excess of transfers of NPN
† Values corrected for anabolism and catabolism of protein

TABLE IX

External, extracellular, and cell balances in subjects receiving NH_4 and K cycle resins together with ACTH or cortisone

Subject	Time (Days)	Therapy			External bal.				Extracell. bal.			Cell. bal.			
		Resin		ACTH											
		NH_4 (g./d.)	K	(mgm./d.)	Cl (meq.)	Na (meq.)	K (meq.)	N (g.)	H_2O (l.)	Na (meq.)	K (meq.)	N* (g.)	Na (meq.)	K (meq.)	K† (meq.)
BS	0–5	48	12	300	−190	−280	−142	−40.8	−1.8	−277	−13	−40.8	− 3	−129	− 32
	5–11	0	0	300	+ 18	− 79	− 31	−35.7	+0.3	− 3	+10	−39.9	− 76	− 41	+ 54
BM	0–7	48	12	100	+ 8	+ 2	+290	+15.3	−0.1	− 3	−11	+16.1	+ 5	+301	+263
JM	0–7	48‡	12	300	−104	−218	−229	−68.5	−0.6	− 48	−13	−70.6	−170	−216	− 48

* Balance of N in excess of transfers of NPN
† Values corrected for anabolism and catabolism of protein
‡ Received H cycle resin instead of NH_4

ments observed in the control studies. This same difference was still present in those of our patients who took comparable amounts of the resin while being treated with medications which replace or augment some of the effects of the adrenal cortex (Table VI).

E. Balance data during the ingestion of acidifying and non-acidifying resins without and with hormones or steroids

The information available on external exchanges is limited by the incompleteness of intake data in the studies in which equal amounts of hydrogen and potassium form resin were given but is nonetheless quite clear on the following four points (Table VII): *a*) with but one exception periods characterized by ingestion of these particular resin mixtures were also characterized by positive balances of potassium; *b*) in general, the retained potassium entered the cellular or, more accurately, the extrachloride space; *c*) the sodium balances were still positive despite resin intake in the subject receiving significant amounts of these electrolytes (DL, periods 6–9 and 9–11 in Table VII) from dietary sources; and *d*) this resin mixture did not accelerate the losses of sodium, chloride, and water already evident in subject DY on essentially complete sodium restriction (Table VII).

The next four experiments listed in Table VIII represent studies in which the smaller amounts of a potassium cycle carboxylic cation exchanger, 12 to 15 g., were added to a daily intake of 45 to 48 g. of the ammonium cycle resin. On this mixture the external balances of potassium were positive in three of the four experiments in which adequate intake data are available, even though the experimental periods were only three to seven days long. Similarly, the balances of both sodium and chloride were negative only in RT, whereas FC retained sodium without chloride.

In the final set of studies in Table IX (patients BS, BM, and JM), in which intake data are available during combined ACTH or cortisone and resin therapy, the external exchanges of potassium, sodium, and chloride followed the variable patterns observed in the 80:20 studies in subjects not given either the hormone or the steroid, but there was a greater incidence of negative potassium and sodium balances, with all subjects losing potassium from their extracellular fluid. It will also be recalled that these patients as a group developed hypokaliemia.

DISCUSSION

It is readily evident from the above results that we can speak only of trends and implications. First, our data in general indicate that the inclusion of some potassium form resin in a resin mixture will mitigate or cancel the losses of endogenous potassium which result when either the hydrogen or ammonium cycle exchangers are used alone for the purpose of reducing sodium absorption. It is obvious that this effect will be observed only if the potassium present on and in the resin is replaced by another cation and thereby made available for absorption. That this does occur to a variable degree cannot be denied. It seems reasonable to suggest, moreover, that the provision of an ade-

quate intake of potassium could perhaps be achieved with greater assurance simply by giving potassium salts at appropriate times during resin therapy. In addition, such an alternative would relieve the patient of some of the burden of ingesting the large amounts of resin currently necessary for the removal of clinically significant amounts of sodium (9). Be that as it may, the trend at present seems to be toward admixtures of the potassium charged exchangers with the ammonium or hydrogen form resins (10–12). It behooves us, therefore, to continue to examine our data on this point as critically as possible. Such scrutiny indicates that if the intake of the potassium form of the resin is achieved at the expense of the hydrogen or ammonium form, the efficiency of the mixture in augmenting stool sodium decreases. This is suggested in the comparisons of the 50:50 and the 80:20 mixtures. Furthermore, it should be noted that as a consequence this is a relatively inefficient way of giving potassium since a large proportion of the ingested ion reappears in the stools. This presumably reflects the greater affinity of the carboxylic exchanger for this ion as compared with sodium (13–17), but it may also be a manifestation, in part at least, of the preponderance of potassium in formed stools (18).

The above statements apply as well to the studies conducted in patients undergoing treatment with ACTH or with cortisone. It has been established in a sufficiently extensive series that these last two agents, alone or in combination, do not alter the electrolyte or nitrogen content of formed stools (19). Hence it is not surprising that the administration of resin mixtures to such patients also increases stool sodium and potassium by amounts comparable to those noted in subjects not receiving ACTH or cortisone. The net effects of such resin mixtures have been used in attempts by us, as indicated by the results in Table IX, to cancel or retard the trends to sodium retention and to potassium deficits mediated through the renal effects of the adrenocortical steroids. It seems likely that larger proportions of potassium resin should prove more efficacious.

The serum data need but little comment. The replacement of progressively larger amounts of an acidifying form of the resin with a non-acidifying congener does of course minimize the tendency to acidosis and hypochloremia. The degree to which this proves effective will depend not on the proportion of the two resins but on the total amount of acidifying resin ingested. Hence the end effects do not represent a cancellation of the acidifying effects of certain forms of the resin.

The emphasis on prevention or mitigation of the acidosis by means of resin mixtures has several sequellae, some of which may prove undesirable. Thus we have already discussed the decreased effect on stool sodium. Also, evidence is available that the acidosis produced by the resin facilitates delivery of edema. Finally, if the acidosis and hyperchloremic effects are lost, they cannot be used to counteract (leaving aside for the moment the question of whether or not this serves any useful purpose) the opposite changes which appear in prolonged cortisone or ACTH therapy.

Finally a word of warning is in order, since under some circumstances any procedures which augment body potassium stores are contraindicated. This is particularly true in those patients with renal failure and a tendency toward potassium accumulation (20–22). It may be predicted with assurance that such subjects would be harmed by therapy with potassium cycle exchanger, since toxic levels of this cation would be reached that much sooner. This danger of course would not be present in patients with normal or even an increased ability to excrete potassium (23–25). From the practical point of view, however, it would be well not to use the potassium cycle exchanger in any patient with renal failure until the adequacy of the renal mechanisms for the disposal of excesses of this cation has been established.

SUMMARY AND CONCLUSIONS

Hydrogen or ammonium form carboxylic cation exchangers have been mixed with the potassium form of the resin in various proportions and administered to patients:

1. The acidosis and hyperchloremia do not appear in short-term therapy with 1:1 mixtures in which the total dosage is 60 g. or less, and yet stool sodium is increased to some extent.

2. With 4:1 mixtures in which the acidifying resin predominates, acidosis and hyperchloremia develop and the output of stool sodium rises well above control values. This is also true of stool

potassium indicating that only part of the potassium form resin has exchanged for cations other than potassium.

3. With the addition of the potassium form resin to hydrogen or ammonium forms, the external balances of potassium are generally positive in all of the mixtures tested.

4. The effects of the resin mixtures on the composition of stools were still evident in patients receiving ACTH or cortisone.

5. The clinical utility of these particular resin mixtures in preventing or deferring the sodium retention, the potassium depletion, the hypochloremia and the alkalosis of prolonged ACTH or cortisone studies has been discussed. The danger of inducing potassium depletion during such therapy, if a sufficiently large intake of potassium is not provided, has been emphasized.

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SODIUM RESTRICTION AND CATION EXCHANGE RESIN THERAPY IN NEPHROTIC CHILDREN

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Programs of prevention or therapy of edema in nephrotic children in use at present still fail to resolve a number of problems. Thus the efficacy of repeated plasma or serum albumin infusions carries with it dangers of reactions as well as certain economic burdens (1–3). Plasma substitutes such as gelatin, polymerized glucose ("Dextran"), or polyvinyl pyrrolidone ("Periston"), have not received sufficiently prolonged clinical trials to exclude the possibility of sequellae such as those which follow acacia therapy (4–7). Similarly, certain practical obstacles attend the application of instruments available for vivodialysis, even when they function efficiently in reducing extracellular volume. Alternative approaches to the therapy of edema such as the infusion of sodium and potassium salts, the use of osmotic diuretics, the injection of nitrogen mustard, the administration of cortisone or of ACTH or the exposure to febrile infections, particularly rubeola, have been only sporadically successful (8–16). Finally, even though complete elimination of sodium from the intake may control edema, such rigid dietary restriction is not acceptable to many patients. It has therefore seemed desirable to us to try one member of a group of agents, the cation exchangers, recently made available for clinical testing. These polymers, ingested by mouth in an appropriate cycle, increase the stool excretion of sodium and of potassium (17–19). The studies which were conducted have provided answers to the following questions: *a*) is the medication sufficiently acceptable to permit prolonged therapy, *b*) how effective is it in abstracting cations from the diet and from body fluids, *c*) does it enhance the loss of edema which can be achieved by sodium restriction alone, and *d*) does its administration entail undue hazards to the patient?

MATERIALS AND METHODS

A carboxylic cation exchange resin in the hydrogen cycle was administered during a total of 15 periods three to six days long to four edematous nephrotic children. With few exceptions sodium intake was markedly restricted, *i.e.*, to 1 to 3 meq./day prior to, during and after resin administration. The diet consisted of a low-sodium milk ("Lonalac") with added milk protein ("Protinal") and carbohydrate (beta-lactose) and contained adequate amounts of calories and nitrogen as well as considerable amounts of chloride and potassium.[1] The patients received in addition, 0.6 to 0.9 g. of ferrous sulphate and maintenance vitamins each day. Water was allowed as desired. Changes during and following resin therapy have been compared with those observed in the same subjects during control periods on sodium restriction alone. Balance procedure, analytical techniques and methods of calculation have been described earlier (20–23). Findings are expressed when possible in statistical terms. Protocols are presented in the appendix.

RESULTS

Attempts to maintain the daily intake of the resin at 30 to 40 g., amounts readily taken by essentially healthy children in control studies (20), were only partially successful. As a result the mean daily intake proved to be only 17.7 ± S.D. 12.4 g. Despite this relatively low dosage certain clearly evident changes appeared in these subjects as a group. These are reviewed and then the stool findings are compared with those following replacement of the low-sodium regimen by a full diet.

A. Resin effects during the essentially sodium-free regimen

From the original data in Table I and the statistical summary in Figure 1 it is evident that with

[1] Composition of formula: "Lonalac" 125 g.; "Protinal" 30 g.; β-lactose 25 g.; sucrose 15 g.; diluted to 1000 ml. with water. Final concentration of sodium 1.1 meq./l.; potassium 44.9 meq./l.; chloride 18.5 meq./l.; nitrogen 8.2 g./l.

resin ingestion the serum carbon dioxide content decreased on the average 4.10 meq./l. (9.10 vol. %) below control values and returned to previous levels following cessation of therapy. This was not accompanied by a rise in mean serum chloride of the type observed with the acidifying cation exchangers in previous animal and human studies (20–21), even though in the post resin period a statistically significant drop in the opposite direction did occur. The only other measured serum constituent to show change was potassium. The average levels diminished by almost 1 meq. during therapy and subsequently returned to pretreatment values.

Stool potassium excretion (Figure 2 and Table II) rose during resin ingestion above rates characteristic of the control and post resin periods in these patients, irrespective of whether it is expressed in terms of milliequivalents per day, milliequivalents per 100 g. of stool or milliequivalents per gram of nitrogen. At the same time urinary excretion of this cation fell off significantly (Figure 2, based on urine data in Table II). The fact that the external balance of potassium did not vary discernibly during those alterations supports the view that these stool and urine potassium changes tended to cancel one another. The lower urinary excretion of potassium persisted into the post resin periods (Figure 2).

Insofar as sodium is concerned, keeping in mind that these patients were on an intake markedly restricted as to sodium content, there is no consistent evidence that stool sodium rose significantly; only the excretion per 100 g. of stool nitro-

TABLE I

Body weight and analyses of blood and serum in nephrotic children receiving the H cycle resin

Subject	Time	Therapy	Body Wgt.	Blood		Serum							
(Age-Sex)	(days)	(g./d.)	(kg.)	Sugar (mgm%)	NPN (mgm%)	HCO_3 (meq./l.)	Cl (meq./l.)	Na (meq./l.)	K (meq./l.)	Ca (mgm%)	P (mgm%)	H_2O (g./l.)	Protein (g.%)
													A:G
RF	0	0	22.6	-	92	23.1	105.1	139	5.3	8.1	5.4	929	
6 M	0-3	0	23.0	-	30	22.9	105.3	138	4.6	-	-	933	
	3-6	0	19.8	-	25	23.6	105.1	139	4.5	8.0	5.0	937	0.8:3.3
	6-9	0	18.9	-	29	23.1	105.1	130	4.6	8.4	5.7	934	0.8:3.8
	9-12	0	18.4	-	32	22.5	104.1	134	5.2	-	-	-	0.7:4.0
	12-15	33	17.0	-	36	14.9	106.0	133	4.8	-	-	925	
	15-18	18	16.8	-	37	17.1	102.6	133	3.3	8.3	6.2	928	0.7:4.0
	18-21	0	17.0	-	32	23.7	99.0	137	3.8	-	-	931	0.7:4.0
	21-24	0	17.2	-	33	24.0	97.8	133	5.4	8.2	-	-	0.3:4.2
	50	0	-	-	39	21.4	103.0	133	5.1	9.2	-	926	0.6:4.0
	50-56	17	-	-	36	16.9	114.2	133	3.6	-	-	936	
	56-58	14	-	-	29	14.7	114.3	135	3.9	-	-	937	
KH	0	0	16.6	-	40	16.7	102.3	131	5.8	-	-	-	0.2:3.2
3½ F	0-6	0	16.4	98	35	18.4	105.7	134	5.9	7.9	6.0	940	
	6-12	10	15.8	-	36	20.3	109.4	136	4.9	7.7	5.6	951	
	12-19	1	15.8	94	34	18.7	108.4	137	3.7	7.6	5.5	950	
	19-22	2	16.0	90	45	18.3	105.9	145	5.1	6.5	6.8	938	0.4:2.9
	22-25	0	15.8	113	46	20.4	106.5	140	5.4	6.6	5.2	942	0.1:3.2
DW	0	0	16.8	73	86	13.2	113.8	136	4.1	7.2	4.3	908	0.6:2.6
6 M	0-7	9	16.3	-	64	3.3	110.1	135	3.1	7.1	3.0	-	0.8:3.2
	8	0	14.2	78	68	7.6	110.2	142	2.5	6.7	3.2	908	0.8:3.6
	7-14	0	-	84	68	10.0	102.5	123	2.6	5.5	3.6	903	
DT	0	0	30.2	85	31	19.8	106.9	142	4.4	-	5.3	931	
12 M	0-7	0	29.8	-	32	19.7	110.8	138	4.7	7.6	6.1	929	0.3:3.0
	7-10	14	29.4	-	-	20.1	111.0	133	5.1	-	-	-	
	10-13	14	29.2	-	31	20.9	108.8	134	4.2	7.0	4.4	916	0.1:4.2
	13-17	0	29.2	-	31	25.0	101.6	137	4.1	-	-	913	
	17-19	0	29.0	-	30	26.3	106.5	147	4.3	7.1	4.4	923	0.6:3.5
	19-22	0	28.4	-	45	26.8	104.4	138	4.3	-	-	916	0.2:4.2
	22-25	0	29.4	-	29	24.4	100.6	134	4.6	7.7	5.1	920	0.5:3.7
	25-28	0	29.3	-	28	22.7	104.3	137	4.0	7.6	4.5	-	0.3:3.5
	28-31	21	29.8	-	36	17.9	110.8	139	4.2	-	-	927	
	31-33	0	30.2	-	38	18.9	101.0	138	3.8	7.2	5.2	935	0.2:3.6
	33-36	0	30.2	-	35	20.8	110.4	137	3.7	-	-	-	-
	36-39	0	29.2	-	31	22.5	109.9	139	4.3	8.1	4.3	929	0.4:3.8
	65	0	30.2	86	39	19.9	107.4	136	3.9	-	4.5	929	0.4:3.5
	65-70	33	29.2	-	35	14.0	115.5	133	3.1	-	-	923	
	70-76	40	30.2	-	34	-	113.6	148	3.5	7.9	4.4	-	0.6:4.1
	110	0	31.4	91	40	20.6	109.7	144	5.1	7.4	4.3	930	0.4:3.4
	110-117	17	30.8	-	48	16.2	106.7	143	3.5	6.4	6.9	-	0.7:2.4
	117-121	0	28.4	-	47	19.8	104.1	145	3.2	7.2	5.4	926	0.5:3.5

gen increased without change in the other two categories. Even this isolated change, however, is of too small magnitude to represent any substantial influence of the exchanger on stool sodium. Neither did the urinary excretion of this electrolyte fall off significantly, though the mean values proved to be somewhat lower. These essentially negative findings are further supported by the observations that the fluctuations in the external and internal balances of sodium did not show, as will be seen later, any real trend which could be attributed to resin.

The small change in the daily stool chloride excretion in the per day and per gram of nitrogen categories, and the lowered urinary output of this ion during resin therapy remain unexplained (Figure 2). These stool chloride changes may merely reflect the limited number of control observations available prior to therapy, but comparison of them with a much larger group of samples obtained in control studies in subjects on an identical regimen (20) reveals the same difference. Whatever the reason may be, the stool changes are of too small magnitude to have any influence on the daily transfers of this anion or of nitrogen. On the other hand, insofar as the lowered urinary chloride values are concerned, it is conceivable that they appeared secondary to decreased potassium excretion. Against this is the finding that in the post resin periods still characterized by the lowered potassium excretion such a relationship cannot be postulated. It is more likely that renal retention of chloride is related to acidosis (21).

Perusal of the summarized mean balance values during the pre and post resin periods (Figure 3) clearly indicates that a low-sodium regimen of the type herein described may by itself induce negative external balances of sodium and of chloride with a

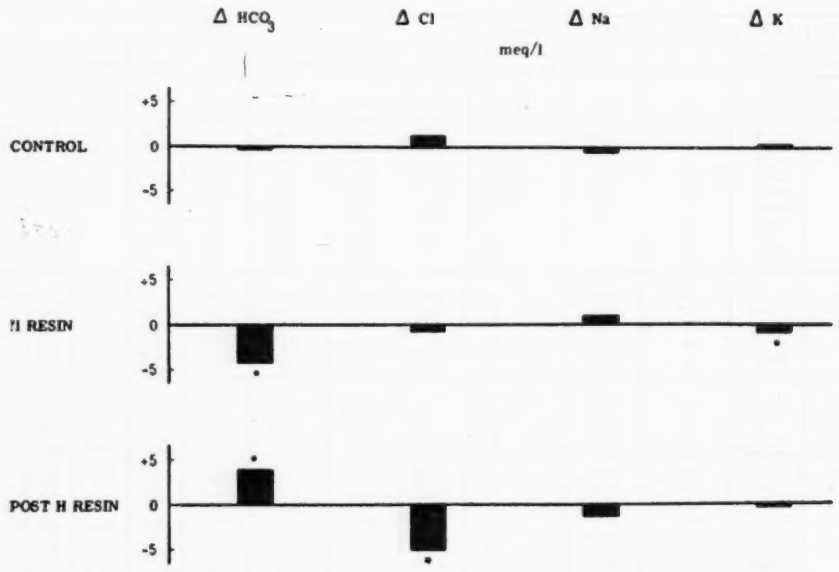

FIG. 1. MEAN CHANGES IN SERUM CONCENTRATION BEFORE, DURING AND AFTER RESIN THERAPY

Fluctuations in serum constituents (Δ HCO_3, Cl, Na, and K) during and following H form resin ingestion have been compared statistically and graphically with those recorded prior to therapy. Asterisks identify mean values found to have a "p" for the "t" test of less than 0.05, and indicate therefore a statistically significant difference. Resin administration reduced the serum bicarbonate content with subsequent restitution during the post H resin periods. The chloride did not change significantly until the resin had been withdrawn at which time a significant decline was observed. The only other change of note was the decrease of 0.93 meq./l. in the mean serum potassium concentrations (S.E. ± 0.31).

decrease in extracellular volume, diuresis, and a loss of body weight. Furthermore, the rates of extracellular sodium and water loss, and of fall in body weight characteristic of the control periods on low-sodium therapy only, were not visibly accelerated by these amounts of resin. Strength is added to these interpretations by noting that the patients were in positive nitrogen balance during the control and resin periods and hence the losses in body weight cannot be attributed to inadequate intake. In the post resin period the nephrotic children took insufficient amounts of milk and developed negative external and cell balances of nitrogen (Table III and Figure 3).

B. Effects associated with resin intake during an unrestricted diet

During days 50 to 58 in BF and 65 to 76 in DY, the low-sodium regimen was replaced during continued resin ingestion by a full diet containing ordinary amounts of sodium (Table II). Though complete balance data are not available and the observations are limited to three in number it should be pointed out that in each instance the patients ate well and took larger amounts of resin. The daily stool sodium and potassium output exceeded by a wide margin values observed in a large series of control subjects on comparable diets without resin (20), and unquestionably exceeded greatly the stool sodium values seen in these same patients while on resin and a low-sodium diet. Chloride and nitrogen output, on the other hand, were not unusual. It is clear, therefore, that in these subjects, as in others (21), the resin can increase stool losses of sodium and, of course, of potassium as well during periods in which sodium is present in the diet.

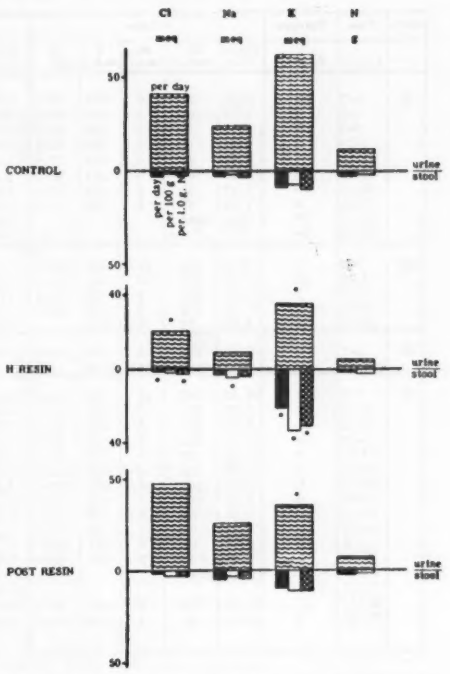

FIG. 2. ELECTROLYTE AND NITROGEN EXCRETION IN URINE AND IN FECES BEFORE, DURING, AND AFTER RESIN THERAPY

Statistically significant increases or decreases from control mean values are marked by an asterisk. It is readily evident that as stool potassium increased, the urinary output of this electrolyte declined. The lowered output of potassium in urine persisted during the post resin period. Changes in stool chloride and in stool sodium were limited to one or two of the categories in contrast to the uniformity of the stool potassium data. Urinary chloride excretion was low during the resin ingestion periods.

C. General comments and clinical course

All four of the patients continued to deliver their edema with only occasional interruptions irrespective of whether or not they were receiving the cation exchanger.

The nonprotein nitrogen of the blood returned to normal in BF, fluctuated between elevated and non-elevated concentrations in KM, remained high in DW, and rose to azotemic levels in DY (Table I). The patient with the most pronounced reduction of serum carbon dioxide content (DW) developed over-breathing on the seventh day of hydrogen form resin therapy coincidental with a respiratory infection, even though he had taken only 9 g. each day. This responded promptly to therapy with parenteral sodium bicarbonate preceded by calcium gluconate and antibiotics. Despite the hypocalcemia present in this child and in the others none of the patients developed tetany during resin therapy. This fact, together with the slight elevations, if any, in serum phosphorus indicate that the low serum calcium values were pri-

TABLE II

Intake data and urine and stool output in nephrotic children receiving the H cycle resin

Subj.	Time	Therapy	Intake					Urine						Stool				
	(days)	(g./d.)	Fluid (l.)	Cl (meq.)	Na (meq.)	K (meq.)	N (gm.)	Vol. (l.)	Cl (meq.)	Na (meq.)	K (meq.)	TN (gm.)	NPN (gm.)	Wgt. (gm.)	Cl (meq.)	Na (meq.)	K (meq.)	N (gm.)
RF	0-3	0	6.15	94	6	229	27.0	3.48	109	9	173	20.1	16.4	607	-	17	52	4.2
	3-6	0	5.41	90	5	220	25.9	3.71	249	211	163	14.6	13.1					
	6-9	0	5.47	94	6	229	27.0	2.75	189	176	88	7.6	7.0	685	13	5	71	5.2
	9-12	0	5.31	90	5	220	25.9	2.88	144	63	176	18.9	17.4					
	12-15	33	6.82	94	6	229	27.0	3.65	69	0	98	14.9	13.5	499	5	34	241	5.2
	15-18	18	5.85	63	4	153	18.0	3.72	42	0	12	16.9	14.7					
	18-21	0	5.97	94	6	229	27.0	4.05	73	0	64	18.6	15.6	880	6	3	104	9.8
	21-24	0	7.07	94	6	229	27.0	5.52	86	23	216	23.8	20.9					
	50-56	17	Full	diet				3.80	50	7	68	23.1	20.2	345	2	68	112	2.8
	56-58	14	"	"				1.03	38	3	18	9.4	7.9					
KM	0-6	0	8.36	190	11	451	54.2	-	-	-	-	-	-	905	19	12	47	7.9
	6-12	10	7.21	178	10	423	50.9	1.84	98	7	103	29.1	24.9					
	12-19	1	6.94	151	9	358	43.1	1.95	111	9	156	36.8	33.9	746	15	14	343	7.8
	19-22	2	4.21	100	6	238	28.6	0.95	54	3	71	17.2	15.8					
	22-25	0	3.84	85	5	201	-	1.75	46	0	74	33.8	33.5	196	1	5	26	1.6
DW	0-7	9	8.99	101	6	244	28.8	5.58	125	79	198	21.3	17.0	107	0.4	5	48	1.2
	7-14	0	Full	diet	("salt	free")		5.60	227	286	67	15.5	10.9	80	3	3	21	0.9
DT	0-7	0	14.26	206	12	500	59.0	9.20	239	0	443	49.4	37.5	837	11	10	44	6.1
	7-10	14	8.35	121	6	256	25.5	6.62	187	62	212	19.6	18.5	923	11	10	82	5.9
	10-13	14	8.25	134	6	269	25.5	7.25	249	93	202	24.6	18.8					
	13-17	0	7.25	180	7	359	36.0	5.35	271	52	289	34.6	27.5	864	6	4	99	8.8
	17-19	0	3.31	87	4	173	17.3	1.95	72	12	105	11.7	9.1					
	19-22	0	6.04	132	6	264	108.2	6.20	148	22	243	66.8	61.6					
	22-25	0	9.11	134	6	267	108.9	3.60	108	11	213	106.9	83.3	1049	1	9	65	9.0
	25-28	0	6.16	128	5	253	116.2	3.60	75	9	179	75.2	57.6					
	28-31	21	6.52	80	5	188	33.6	5.30	64	15	189	30.8	24.4	384	0	11	146	5.3
	31-33	0	3.23	23	1	56	10.3	3.30	68	0	122	22.1	17.4					
	33-36	0	6.48	65	4	157	28.7	4.39	170	99	157	23.8	18.8					
	36-39	0	5.08	88	5	212	39.0	5.20	339	246	206	34.8	28.2	1063	17	78	52	10.9
	65-70	33	Full	diet				14.45	1012	636	301	59.8	47.7	1444	5	347	173	7.6
	70-76	40	"	"				10.98	971	720	191	62.4	54.6	1179	8	148	176	6.1
	KD-117	17	14.32	150	9	363	66.7	10.80	268	175	284	66.9	58.0	804	5	47	114	9.8
	117-121	0	8.10	64	4	156	28.6	8.10	427	363	198	42.8	33.8	677	1	23	13	3.4

TABLE III

External, extracellular, and cell balances in nephrotic children receiving the H cycle resin

Subject	Time	Therapy	Ext. Bal.				Extracell. Bal.			Cell Bal.			
	(days)	(g./d.)	Cl (meq.)	Na (meq.)	K (meq.)	N (gm.)	H_2O (l.)	Na (meq.)	K (meq.)	N* (gm.)	Na (meq.)	K (meq.)	K** (meq.)
RF	0-3	0	-	- 16	+ 30	+ 4.7	-0.1	- 27	- 7	+ 4.7	+ 11	+ 37	+ 26
	3-6	0	-	-217	+ 31	+ 9.1	-1.3	-175	- 7	+ 9.9	- 42	+ 38	+ 14
	6-9	0	-102	-174	+105	+16.8	-0.9	-185	- 4	+16.3	+ 11	+109	+ 70
	9-12	0	- 62	- 63	+ 8	+ 4.3	-0.5	- 45	+ 1	+ 3.9	- 18	+ 7	- 2
	12-15	33	+ 21	- 12	+ 10	+ 9.5	0	0	- 1	+ 9.0	- 12	+ 11	- 10
	15-18	18	+ 17	- 15	+ 21	- 1.6	+0.4	+ 55	- 9	- 1.7	- 70	+ 30	+ 34
	18-21	0	+ 17	+ 3	+113	+ 3.5	+0.4	+ 79	+ 6	+ 4.0	- 76	+107	+ 97
	21-24	0	+ 3	- 21	- 40	- 1.8	+0.1	- 18	+12	- 1.9	- 3	- 52	- 48
KM	6-12	10	+ 77	- 5	+192	+18.4	+0.5	+ 54	- 5	+18.4	- 59	+197	+153
	12-19	1	+ 32	- 9	+ 52	+ 2.3	+0.3	+ 67	- 7	+ 2.3	- 76	+ 59	+ 53
	19-22	2	+ 42	- 3	+103	+ 9.4	+0.4	+132	+12	+ 9.4	-135	+ 91	+ 71
	22-25	0	+ 37	- 2	+100	-	+0.3	- 6	+ 4	-	+ 4	+ 96	-
DW	0-7	9	- 26	- 80	- 1	+ 6.2	-0.1	- 17	- 4	+ 8.6	- 63	+ 3	- 18
DT	0-7	0	- 47	- 1	+ 13	+ 3.3	-0.7	-138	- 1	+ 3.1	+137	+ 14	+ 7
	7-10	14	- 74	- 64	+ 3	+ 2.7	-0.7	-132	0	+ 2.7	+ 68	+ 3	- 3
	10-13	14	-123	- 95	+ 26	- 2.2	-0.9	-107	-10	- 2.0	+ 12	+ 36	+ 41
	13-17	0	- 97	- 51	+ 4	- 4.8	-0.4	- 17	- 2	- 4.8	- 34	+ 6	+ 17
	17-19	0	+ 10	- 13	+ 35	+ 2.4	-0.1	+ 25	0	+ 2.6	- 38	+ 35	+ 29
	19-22	0	- 18	- 22	- 1	+38.2	-0.1	- 67	0	+35.4	+ 45	- 1	- 85
	22-25	0	+ 24	- 11	+ 32	- 1.2	+0.5	+ 41	+ 4	+ 1.8	- 52	+ 28	+ 24
	25-28	0	+ 51	- 11	+ 52	+35.4	+0.2	+ 46	- 4	+35.6	- 57	+ 56	- 29
	28-31	21	+ 13	- 20	- 89	- 0.4	-0.3	- 30	0	- 1.9	+ 10	- 89	- 84
	31-33	0	- 48	- 7	-125	-14.0	+0.3	+ 23	- 2	-14.4	- 30	-123	- 89
	33-36	0	-116	-137	- 26	- 0.8	-1.5	-212	- 6	- 0.2	+ 75	- 20	- 19
	36-39	0	-262	-283	- 20	- 1.2	-	-	-	-	-	-	-
	110-117	17	-126	-217	- 35	-10.2	-0.7	-126	-17	-11.8	- 91	- 18	+ 10
	117-121	0	-367	-406	- 55	-17.8	-3.1	-408	-12	-17.6	+ 2	- 43	- 1

* Corrected for balance of NPN

** Corrected for K associated with intracellular metabolism of N

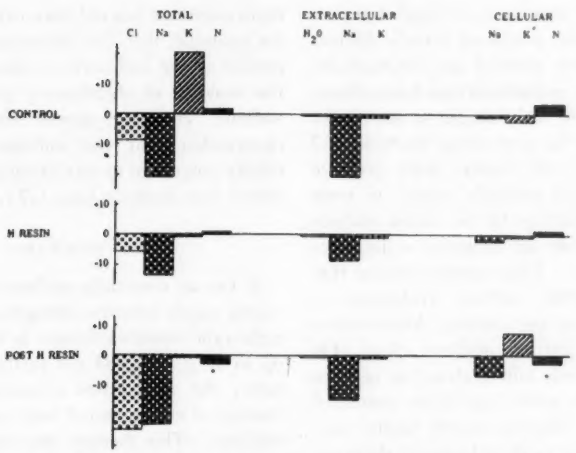

FIG. 3. EXTERNAL ("TOTAL") BALANCES OF ELECTROLYTES AND OF NITROGEN PARTITIONED INTO EXTRACELLULAR AND CELLULAR COMPONENTS

The graph presents the mean values during control, resin, and post resin periods. The asterisk indicates that, compared to the controls, statistically significant differences were present only in the external and cell balances of nitrogen during the post resin periods. It is obvious that on sodium restriction alone in the control periods the patients continued to lose sodium, chloride, and extracellular water throughout at essentially the same rate, as indicated by changes in the chloride space. In the control periods considerable amounts of ingested potassium were retained. This element entered cells with nitrogen since the overall cellular balance of K was positive but K′, which refers to transfers of potassium in excess of metabolism of protein, was negative. However, the scatter of values in this and in the subsequent periods resulted in considerable overlap and the "p" value was not within the limits set for statistical significance.

marily a manifestation of the remarkably reduced concentrations of serum albumin (Table I) present before, during, and after resin administration. Taking serum potassium values above 5 meq./l. as suggestive of potassium retention secondary to renal insufficiency, the data on BF, KM and DY indicate the ability of the resin to lower the serum and extracellular fluid concentrations of potassium. This same effect resulted in hypokaliemia in DW.

The serial studies of erythrocyte and leucocyte counts, urine protein output, urine specific gravity, or of phenolsulphonethalein excretion did not reveal any untoward effects induced by the resin therapy. As a matter of fact the trend was toward improvement. The end result in this group to date consists of one death (DW) and three remissions, four to six months in length; obviously the survivals cannot be ascribed to resin therapy.

DISCUSSION

A practical aspect of resin therapy in nephrotic children deserves first comment. Our subjects experienced considerable difficulty in ingesting and retaining the desired amounts of the cation exchanger. Various vehicles were tried with negligible success; capsules proved to be in general more acceptable. Other essentially healthy children on the same ward on a similar regimen at the same time took the prescribed amounts of resin with only minimal objections. It should be pointed out that in general, patients on an unrestricted diet tolerated the resin much better and took larger amounts than those on the milk formula. Irrespective of whichever reasonable explanation is advanced for this difference its reality and therapeutic importance, at least in this small group of patients, cannot be denied.

Though it is true that resin therapy superimposed on this regimen produced certain distinct changes, none of them exerted any dramatically beneficial effect. The patients did not lose sodium, extracellular water, or body weight at any faster rate. Furthermore, the post resin anorexia and voluntarily lowered milk intakes with negative nitrogen balances were probably related to resin treatment. These findings by no means exclude the possibility that resin can be useful in the treatment of edema states. They merely indicate that *if essentially complete sodium restriction is achieved, this resin in the amounts herein taken apparently cannot exert any additive effect.* On the other hand it is only fair to state that perhaps the resin through its acidifying effects permitted the continuation of diureses which might have otherwise ceased. It is evident, however, that even though endogenous sodium cannot be removed in significant quantities by resin in these amounts during almost complete sodium restriction, the exchanger certainly did increase stool losses of sodium during a diet which contained ample amounts of this cation. Whether or not these increments prove to be of sufficient magnitude to influence the net external balances of the ion and thereby prevent or correct edema will obviously in great measure depend on the concomitant urinary excretion of sodium.

The potassium data in these studies do suggest that this exchanger, properly used, will deviate exogenous and endogenous potassium to stools. This effect will obviously tend to forestall and to correct potassium intoxication, and its recognized threat to survival, in patients with renal diseases (24–27).

It may be of interest at this point to speculate upon various possibilities whereby the efficiency of these resins could be increased. The difficulties of ingesting sufficiently large amounts might then be resolved, although we have been able to increase, subsequent to the studies described in this paper, the intake of the exchanger by suspending it in flavored cornstarch. The size of the individual resin particles may also be important in determining the clinical efficiency of the resin. Moreover, the influence of certain dietary constituents such as potassium, calcium, and fats upon the ability of the exchange agent to increase stool sodium excretion has not been explored. It may be, for example, that low potassium diets during ingestion of the carboxylic exchanger would permit the removal of significantly greater amounts of sodium. However, against this possibility is the observation that the sulfonic resins removed chiefly potassium in rats maintained on diets completely free of electrolytes (27).

SUMMARY

1. On an essentially sodium-free regimen, providing ample calories, nitrogen, and potassium, a carboxylic cation exchanger in the hydrogen cycle, up to 40 g./day, did not further increase significantly the stool losses of sodium nor accelerate the loss of edema and of body weight in nephrotic children. This therapy may have, however, prolonged the diuresis through its acidifying effects.

2. On a diet which contained considerable amounts of sodium the exchanger raised the stool sodium, thereby indicating the value of this agent in augmenting the excretion of ingested sodium.

3. The resin did increase significantly the loss of potassium via the gastrointestinal tract, but effects of this on the external balances of potassium were in great measure cancelled by a simultaneous reduction in the urinary excretion of the electrolyte. Nonetheless, serial serum potassium studies indicate the resin cancelled trends to hyperkaliemia.

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CASE REPORTS

DW—(CH 4071)—This seven year old white boy was readmitted to Children's Hospital from a convalescent home on 1/23/50 for treatment of persistent edema.

Four years earlier he had become edematous one month after an acute infection. Plasma and blood transfusions had been given without relief. In 1948 there was anasarca, blood pressure 120/62, 4 + albuminuria, serum cholesterol 1216 mgm. %, total protein 3.8 g. %, albumin 0.2 g.% and globulin 3.6 g. %. Fever and respiratory embarrassment had developed which required oxygen, antibiotic therapy and digitalization. Edema was fairly well controlled with ammonium chloride and mercurial diuretics and the patient was sent to a convalescent home. In November 1948 a diet consisting solely of sodium-free dialyzed milk was begun with improvement in clinical condition and subsidence of edema. This regime continued aside from occasional dietary indiscretion.

On admission 1/23/50 there were marked pallor, slight generalized edema, and a soft apical systolic murmur and a BP of 100/65. His hemoglobin was 5.9 g. %, RBC 2.9 million, and WBC 12.7 thousand and his urine contained 2 + to 4 + albumin, granular casts, and occasional red and white blood cells. The cholesterol was 1846 mgm. %; other blood and serum values during his hospitalization are shown in Table I.

The sodium-free milk diet supplemented with vitamins and iron was continued with addition of hydrogen cycle

resin. He accepted an average of only 9 g. of the resin per day for a week. At this time an upper respiratory infection developed, with subsequent nausea, vomiting and acidosis. Improvement occurred during therapy with antibiotics, oxygen, blood transfusion, intravenous calcium gluconate and bicarbonate. On the 20th day tetany developed and was relieved by calcium therapy. This recurred on the 31st and 62nd hospital days. On 4/5/50 he developed congestive heart failure and became irrational; venous pressure rose, and blood pressure fell. Digitalization, oxygen, and supportive therapy were ineffective and the patient died on 4/6/50.

At autopsy, nephrosis, right pleural effusion, ascites, dilatation of right auricle and ventricle, primary atypical pneumonia of unknown origin, congestion of liver and accessory spleen were found.

DY—(CH C817)—This 11 year old Chinese American boy was first admitted 9/6/49 with anasarca, albuminuria, hypercholesterolemia, and hypo-albuminemia. PSP excretion was 60% in two hours. On a low-sodium milk, rice and fruit diet, supplemented with vitamins and iron, edema subsided and the patient was discharged from the hospital. Edema recurred, but after hospitalization and sodium restriction, diuresis occurred and he was sent to a convalescent home.

On 2/18/50 the patient was readmitted with slight facial edema and abdominal fullness, but no peripheral edema. Laboratory findings were essentially unchanged, except that the hemoglobin had fallen to 7.8 g. and the red count to 3.9. Blood and serum clinical data for his entire hospitalization appear in Table I.

Therapy consisted of low-sodium milk diet plus various combinations of cation exchange resins. On the ninth day, 14 g. of hydrogen cycle resin were given and continued for a period of six days. After a six day control period 120 ml. of 40% urea solution were ingested daily for three days. Hydrogen cycle resin was repeated for five days, and milk protein supplement, 60 g./day, was added to the diet. However, the clinical condition of the patient remained unchanged. During this time protein intake was 90 g. daily, with urinary losses of 10–13 g./day. Unexplained abdominal pain and temperature elevations present from the 32nd to the 35th day were treated with penicillin.

On the 66th day he was placed on a general diet with 40 g. of the hydrogen cycle resin daily. There was disappearance of edema and weight loss of 2 Kg. with subjective and objective improvement.

Subsequently resin therapy was repeated from the 110th to the 117th day. No significant change appeared in urine or blood throughout therapy.

BF—(CH 0801)—This six year old negro boy was readmitted 3/6/50 with edema, marked ascites and 3+ albuminuria.

One month earlier he had been admitted with periorbital and pretibial edema, vomiting, abdominal cramps, mild diarrhea, and enlargement of the abdomen of three days' duration. BP was 102/64. There was 3+ to 4+ albuminuria and a few white and red blood cells in the urine. The NPN was 32 mgm. %, total protein 4.3 g. % with 0.7 g. albumin. Cholesterol was 864 mgm. %. The intravenous pyelogram was normal. A diagnosis of nephrosis was made and a low-salt high-protein diet given with improvement. He was discharged 2/24/50.

He was readmitted on 3/6/50 with edema, marked ascites, and 3+ albuminuria. Blood and serum analyses appear in Table I. Hemoglobin was 10.5, RBC 3.6, WBC 7.8 thousand. On a diet consisting exclusively of a low-sodium milk formula the edema diminished rapidly during the first 12 days. From the 12th to the 18th days the patient received hydrogen cycle cation exchange resin. During this time no change in his condition was noted.

Dialyzed milk formula was continued until the 20th hospital day when intake was changed to low-salt diet and hydrogen cycle resin was again given. This regimen was associated with rapid accumulation of edema fluid until it was interrupted on the 34th day by an acute episode of fever, vomiting and severe abdominal distention and pain suggestive of peritonitis. Recovery from this acute episode occurred after four days of antibiotic therapy. On a low-sodium milk formula, diuresis and disappearance of edema occurred rapidly. There was no change in albuminuria.

The child remained on this diet and almost completely free of edema until 6/12/50, when a general diet and 20 g. each of hydrogen and potassium cycle resins were given. Within one week edema appeared in severe degree. A low-sodium milk diet with rice, fruit, and "salt-free" bread was administered for the remainder of his hospital stay. Hydrogen form resin was resumed, and in eight days edema subsided and a weight loss of 1 Kg. occurred. Albuminuria persisted throughout the study.

KM—(CH M6990)—This two year old white girl was admitted 5/6/50 because of persistent edema despite dialyzed milk and salt-free cereal diet.

Two years before there had been swelling of the face, legs, and abdomen of two weeks' duration subsequent to an upper respiratory infection. On admission in 1948 the child was pale, poorly developed, with periorbital and peripheral edema. BP was 120/75. There was 4+ albuminuria, 6 RBC/hpf, specific gravity 1.037. A normochromic anemia and leucocytosis were present. Blood NPN was 30 mgm.%, serum cholesterol 608 mgm. %, albumin 0.4 and globulin 3.7 g. %. Diuretic therapy produced slight improvement.

On 5/6/50 there were generalized edema and hepatomegaly, blood pressure was 105/75, albumin 3+ to 4+, and a few red cells and granular casts were present in the urine. Hemoglobin was 7.5 g. %, RBC 3.2, and WBC 9.1. Excretion of PSP was 50% in two hours.

The patient was fed only low-sodium milk supplemented with vitamins and iron. After one week a slight reduction in facial edema was noted, with weight decrease of 0.8 Kg. Hydrogen cycle resin was then given for a period of 15 days. This was poorly accepted by the patient, only small amounts being taken. During administration of resin there was no change in blood or urine findings. Serum values appear in Table I.

PROBABLE CLINICAL UTILITY OF CATION EXCHANGE RESINS

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The data which have been presented in the previous papers clearly indicate that the carboxylic cation exchange resins in the hydrogen, ammonium, sodium, and potassium forms individually or in combinations increase the stool excretion of sodium and potassium in man and dog (1–4). In the amounts administered however, 20 to 60 g./day, there was only a limited absolute increase in the stool content of sodium and potassium. The *in vivo* efficiency of these exchangers was usually 1 meq. of sodium or less removed per gram of resin ingested when the diet contained sodium. In addition, potassium excretion per gram of the resin was usually about 50% greater than sodium. Although stool sodium was largest during the administration of the sodium form, and potassium greatest during ingestion of the potassium cycle, it seems clear that these ions were actually being supplied to the body because less was excreted in the stool than was administered.

It may often prove possible to utilize these substances, with the exception of the sodium form of the exchanger, to advantage clinically in conditions in which endogenous sodium is already present in excess or in which exogenous sodium is prescribed. It is logical, for example, to expect that in some borderline situations the resin may serve even without dietary restriction to tilt the balance of sodium sufficiently to prevent further retention or to produce an actual loss of previously retained ions via emunctory pathways other than the gastrointestinal tract. Thus it may well be possible to maintain some patients on a full diet plus resin. It naturally follows that others may only need partial limitation of exogenous sodium. However, the composition of the diet influences the efficiency of the resin. When sodium is rigidly withheld, the amount of sodium removed per gram of the exchanger decreases markedly. Our studies suggest that if essentially complete sodium restriction is achieved only small increments of this cation will be removed in the stool per day and prolonged therapy may be required for this route of excretion to attain important effects in the removal of endogenous sodium. This is surprising inasmuch as a large pool of endogenous sodium should be available for interchange with the resin but this presumably reflects the greater affinity of the resin for potassium as compared to sodium (5–10).

Since ordinary full diets provide an intake of some 100 to 300 meq. of sodium in the course of 24 hours, it is evident that these agents used alone in amounts up to 60 g./day are incapable of producing negative balances as a result of losses in stools or of preventing the absorption of a major part of the sodium through the intestine. This is particularly true when it is recalled that in the animal experiments and to a lesser degree in the human studies, deviation of sodium excretion to the gastrointestinal tract was accompanied in turn by reduced urinary losses of this ion. A larger intake of resin might of course shift the sodium balance to the negative side, but unfortunately prescriptions in such dosage too often prove burdensome to most patients. This is particularly apt to be true of those who are ill and already anorexic, nauseated or vomiting.

The effects of the hydrogen and ammonium cycle resins are not limited, however, to deviation of sodium to stools. They both produce an acidosis which in the control of edema can be looked upon as a beneficial and a desirable effect in subjects without impaired renal function. This development can induce diuresis by the same mechanisms responsible for increased urine volumes following acidifying diuretic salts (11). It is probable that the hydrogen or ammonium ion attached to the resin is absorbed into the body fluids following displacement from the resin by the other cations present in enteric juice and thereby produces acidosis. This analogy is supported not only by the well-documented changes following ammonium chloride administration but also by the invariable occurrence of hyperchloremia as a se-

quel to the use of any of the so-called acidifying diuretics (11). It is true, as our own findings indicate (4), that frank acidosis and overbreathing may accompany the ingestion of acidifying resins, especially in patients with far-advanced renal failure. Since it is highly dubious that accentuation of a definite acidosis already present as a consequence of renal insufficiency exerts any further stimulus to urinary sodium and water losses, it is well to identify such patients and treat them either with lesser amounts of resin, or with non-acidifying resins in other cycles, or perhaps both. The evidence on hand indicates, however, that the lessened tendency to acidosis recorded with mixtures of hydrogen and potassium, or of ammonium and potassium cycle resins, merely represents the effect of reducing the amount of hydrogen or ammonium ion administered (3). The potential benefits of such mixtures in this regard are minimized by the relatively decreased efficiency of the potassium-bearing resin with respect to sodium exchange (6–10). Further, it is known that potassium deficits in the body are accompanied by alkalosis and that excessive retention of potassium in cells is of itself productive of acidosis (12, 13).

Again, as in the case of the acidosis which follows the use of hydrogen and ammonium carriers, the frequency with which these agents increase stool potassium losses and produce negative balances of potassium may be either undesirable or desirable, depending on the particular patient under treatment. Thus it has been established in previous studies that losses of body potassium in urine, diarrhea, vomitus, or drainage from the intestinal lumen or from fistulae can result, if adequate treatment is not provided, in undesirable deficits of this important cation (14–21). This depletion can be accompanied by hypokalemia, muscular paralysis and electrocardiographic changes, particularly in the S–T and T segments, and prolongation of the Q–T interval (22, 23). Evidence is also available that losses of cell potassium induced experimentally in animals produce myocardial and muscle cell necrosis (24, 25), and that replenishment of depleted stores decreases the mortality in diarrheal infants (15). In view of these facts any agent which can lower body potassium below normal may produce harm. Therefore, factors such as starvation (16), administration of mercurial diuretics (26), or even ACTH or cortisone (27–29) will increase the requirements of potassium. On the other hand it is obvious that in patients with excessive body stores of potassium this effect would be beneficial (30–32). Certainly ample evidence is available that increased levels of plasma and extracellular potassium will cause cardiac arrest and death (33, 34). This development is most frequently encountered in patients with renal failure, particularly anuria, though it is known to accompany excessive administration of potassium salts (35) and adrenal cortical insufficiency (36), and is even encountered for as yet unexplained reasons in certain newborn infants (37). In some of these patients the hydrogen and ammonium resins can be used to advantage to lower body potassium back toward normal. Admixture of potassium resin would be potentially dangerous in such subjects. It is obvious therefore that the prescription for resin therapy with hydrogen, ammonium, potassium, or any other cycle must be written with these effects and limitations in mind, combined with an adequate knowledge of the patient's status and disease.

Insofar as the sodium cycle resin is concerned little need be said even though it can influence cation balances. Thus in sodium depletion states the administration of sodium salts as such is far more certain (38, 39). The resin could be employed, as indicated by our data, to remove potassium. From the theoretical point of view it might be useful in patients with renal disease or Addison's disease where the combination of potassium excess and sodium deficits coexist (36, 40). Other far more effective modes of therapy are, however, available in Addison's disease (41). In the majority of renal disease states the accumulation of potassium is too often accompanied by impending or actual excesses of sodium to permit use of the sodium cycle resin. It should be emphasized that these generalizations do not exclude the possibility that in isolated clinical situations the characteristics of this resin might be considered to be custom-tailored.

Our experience with the calcium cycle resin is as yet too limited to permit any definite statement. If the conclusions drawn from the hydrogen and ammonium cycle studies are valid it should prove gram for gram less effective in inducing diuresis, since the acidifying effect is absent. This attribute may, however, make it useful in cases with renal

failure if it serves to increase losses of sodium and potassium in stools. In this respect it should be remembered that the calcium released in the exchanges with other cations could conceivably be precipitated with phosphate in the intestinal lumen. This event may be useful in modifying the hyperphosphatemia of renal failure and, directly or indirectly, the hypocalcemia. However, bivalence, high ionic diameter, high atomic weight and position in the electromotive series all make calcium elution, in favor of sodium or of potassium, inefficient (6–10). Furthermore the possibility must be considered that the use of milk formulae, because of their relatively high calcium content, may make the other resins less efficient, since the hydrogen, ammonium and potassium resins will tend to take up calcium in preference to sodium, particularly in situations where the concentration of sodium in the medium is minimal, as is the case with sodium-free milk.

Our patients did not show any recognizable evidence of calcium depletion in the relatively short time they received these resins. This problem as well as the one of negative calcium balances and of hypocalcemia during prolonged therapy is still unanswered, although it would seem to be a definite hazard. In addition hypokaliemia might mask the manifestations of tetany (42), and the acidosis defer its onset (43). It might be difficult to prevent this effect by supplying additional dietary calcium during resin therapy since this would reduce the excretion of sodium and potassium in the stool. Similarly we have no information about the quantitative effects of these resins on magnesium metabolism.

Dock has pointed out that the resins as currently used are at best efficient to the extent of 50% of theoretical capacity (44, 45). A number of possibilities exist whereby resin efficiency might be raised and it may be well to list them briefly here. The simplest measure would be to use smaller resin particles, and experiments are now in progress, employing 200 mesh resin in hopes that this may increase sodium uptake. Further, the medium in which the resin is administered requires study. Suspensions of resin in liquid or semi-liquid form in non-ionic vehicles such as cornstarch might well increase exchange and permit ingestion of larger amounts than presently tolerated in capsules or as a dry powder. Our own data do not include sufficient no-sodium, milk-free cases to evaluate the importance of dietary calcium in blocking resin-acceptors and thus preventing sodium uptake. Finally, it has long been known that ion exchange and uptake is increased by the presence of ethanol in the substrate, leading to the suspicion that a resin elixir might prove to be both effective and acceptable. In addition it may be possible to prevent acidosis resulting from the ingestion and exchange of the ammonium and hydrogen forms by simultaneous administration of an anion exchanger or a salt which would decrease the absorption of or buffer the released ions. It may also be possible to produce resins which contain an organic molecule in the exchange position that would be utilized in large amounts in the body without harmful effects.

In conclusion it seems very clear that these resins provide a valuable additional therapeutic means of controlling body water and electrolytes. Their variety of effects necessitate, however, an adequate understanding of their actions and the status of the patient. It would appear best to prescribe the form of the resin that would most closely meet the needs of the individual, and to periodically determine the various blood constituents during therapy.

At present perhaps the most extensive use of these substances lies in permitting patients requiring salt restriction to ingest a more palatable diet than they could otherwise. The hydrogen and ammonium forms of the exchanger with additional dietary potassium appear to be most useful in patients with edema but with adequate renal function; *i.e.*, congestive heart failure, cirrhosis of the liver, and hypoproteinemia. In addition, *if sufficient potassium is supplied* they may counteract the salt retention, alkalosis and hypochloremia which occur during prolonged ACTH or cortisone therapy.

SUMMARY AND CONCLUSIONS

Some of the newer knowledge available concerning the effects, modes of action and clinical usefulness of the carboxylic cation exchange resins has been reviewed and evaluated. Limitations and possible dangers have been emphasized.

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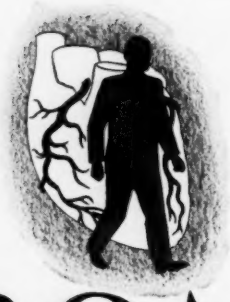

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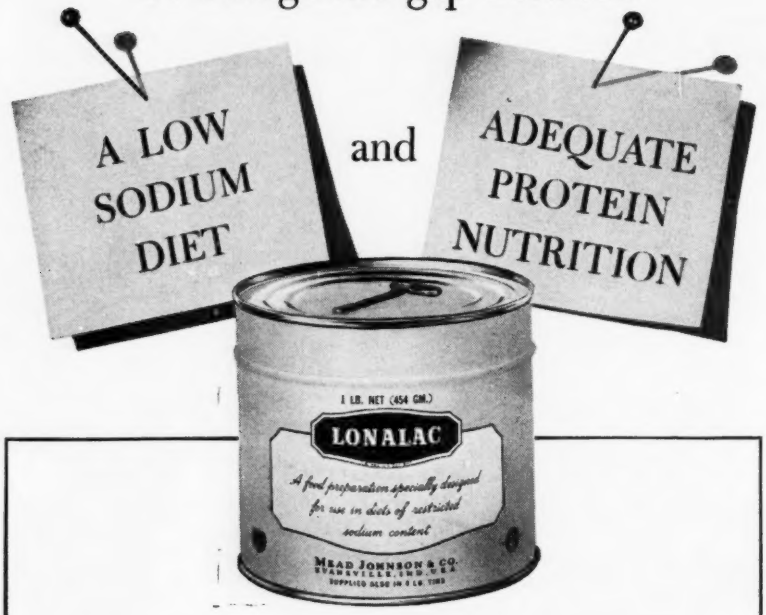
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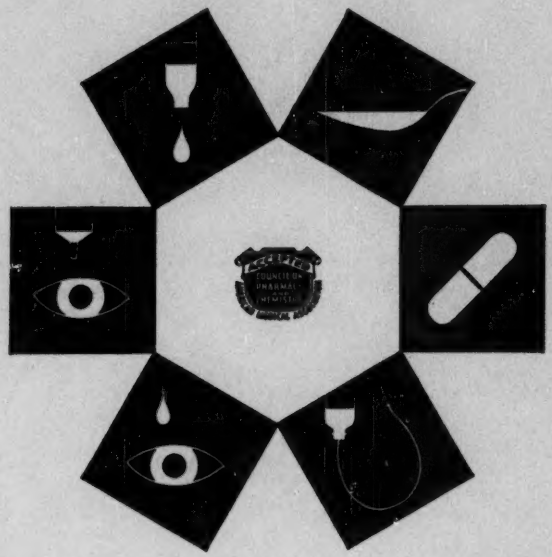

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